as well as dyspnoea is higher in smokers than it is in nonsmokers and it is also higher in the inhabitants of Vlaardingen than it is in those of Vlagtwedde. The $FEV_{1.0}$ showed few differences between smokers and nonsmokers and between the inhabitants of Vlaardingen and those of Vlagtwedde.

*Conclusion*

The data currently available in the literature on the relationship between air pollution and the incidence of respiratory disease are not in accord with one another. This is due, among other things, to the fact that it is difficult to adequately differentiate between the effect of concurrent other provocative factors and that of air pollution The relationship between air pollution and meteorological factors or the climate interferes with many studies on the short-term effects of air pollution. In certain weather conditions which may induce respiratory symptoms (such as the concurrent presence of fog, a calm and sunlight), pollutant particles will not be dispersed but will continue to float over a particular area so that it will be hard to determine which is the (main) cause of an increase in respiratory symptoms. The problems relating to this matter have been described by Cassell et al. (4), among others.

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## APPENDIX V. EFFECT OF PARENTAL SMOKING ON RESPIRATORY SYMPTOMS IN THEIR CHILDREN

Various studies have been conducted on the effects of parental smoking on respiratory symptoms in children.

*Cameron* (1) made a telephone inquiry into the relationship between disease during the week prior to the inquiry and smoking by members of the family in 1 000 families in Denver. The number of patients among smokers and nonsmokers was equal in individuals over nineteen. In those under nineteen, the proportion of patients in smoking families was larger than that in nonsmoking families.

*Cameron* et al. (2) carried out a similar telephone inquiry on smoking habits and disease in 1 000 families in Detroit. They learned that respiratory disease was more common in 0–16-year-old children of smoking families than it was in children of nonsmoking families. This difference was not statistically significant in children under five. The amount of smoke to which the children were exposed in smoking families of sick children was larger than it was in smoking families in which the children were not ill.

*Norman-Taylor* (3) studied the relationship between respiratory infection and parental smoking habits in five-year-old children. In nonsmoking families, 33.5 per cent of the children showed respiratory symptoms. In those families which included heavy smokers (one or several individuals smoking over twenty cigarettes daily), this proportion was 44.5 per cent.

*Colley* (4) examined the relationship between coughing in children in the 6 to 14 year range and parental smoking habits. The number of coughing children was smallest in nonsmoking parents and largest when the two parents smoked. Independently of parental smoking habits, there was a definite relationship between respiratory symptoms in the parents (in which expectoration on arising was adopted as a criterion) and constant coughing in the children. The number of coughing children of smoking parents without respiratory symptoms was only slightly larger than that of nonsmoking parents without respiratory symptoms. The results were obtained by questionnaires completed by the parents.

*Colley* et al. (5) did follow-up studies in 2 205 children in North-West London; the studies started in the first year of life and were continued over a five-year period. Inquiries were made each year regarding pneumonia and bronchitis in the children and smoking habits and respiratory symptoms in the parents. During the first year of life, there was a relationship between the symptoms shown by the children and parental smoking. Bronchitis and pneumonia were more common in children of smoking parents than they were in children of nonsmoking parents. This relationship was absent in children after the first year of life. On the other hand, there was a correlation between respiratory symptoms in the parents (expectoration on arising being adopted as a criterion) and bronchitis and pneumonia in the children. In the first year of life, the hazard of bronchitis and pneumonia in the children was doubled by parental smoking.

*O'Connell* et al. (6) studied the effect of cigarette-smoke on asthma in children. For this purpose, a group of asthmatic patients was compared with a group of controls. Sixty per cent of the parents of the patients were smokers, as was also the case with 60 per cent of the parents of the controls. Smoke caused aggravation of the asthma in 26 per cent of the patients whose parents did not and in 67 per cent of those whose parents did smoke. In the controls smoke was experienced as an irritant of the respiratory tract by 2 per cent of the children whose parents

did not and by 16 per cent of those whose parents did smoke. Of the asthmatic children of non-smoking parents, 2 per cent showed an exacerbation of symptoms after inhaling cigarette smoke. This was the case with 16 per cent of the asthmatic children who had a single smoking parent and with 20 per cent of those who had two smoking parents. A considerable proportion of those asthmatic children whose symptoms were aggravated by cigarette smoke showed fewer symptoms when the parents gave up smoking.

*Harlap* et al. (7) did a prospective study of the number of admissions during the first year of life in children of mothers with known smoking habits. Children of smoking mothers were hospitalized more frequently than were those of non-smoking mothers. Admissions for bronchitis and pneumonia were significantly more common in children of smoking mothers than they were in children of nonsmoking mothers. This was only found to be the case with children from 6 to 9 months of age.

## CONCLUSION

The studies of the relationship between parental smoking and respiratory disease in children showed that:

(1) The effect of parental smoking on respiratory symptoms in children cannot be considered without paying attention to parental symptoms. A differentiation should be made between the effect of parental respiratory symptoms on the children through genetic factors and cross infection and the effect of cigarette smoke.

(2) Symptoms of asthma induced in children by smoke are aggravated more often when the parents are smokers than when they are non-smokers.

(3) The degree of sensitivity to cigarette smoke probably varies with age.

(4) The amount of smoke inhaled has an effect on the symptoms.

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## APPENDIX VI. TABLES 1-26

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Table 1. *Sick absence,[a] comparison of chronic and acute conditions, The Netherlands, 1966, 1963, 1958*

| | Numbers of I.S.C.[b] | 1966 % of total number of days of absence | Average duration per spell of absence (days) M | F |
|---|---|---|---|---|
| *Chronic diseases* | | | | |
| Cardiovascular diseases | 410–416 | | | |
| Diseases of endo-myo- or pericardium | 420–422, 430–432 | 6.9 | 167.1 | 129.1 |
| Disturbances in rate and rhythm | 434 | 0.3 | 68.2 | 68.2 |
| Other heart diseases | | 0.3 | 104.2 | 78.3 |
| Hypertension and arteriosclerosis | | 2.6 | 114.4 | 89.2 |
| Other diseases of the arteries | | 0.6 | 139.1 | 69.6 |
| Total | | 10.7 | 118.6 | 86.9 |
| Respiratory diseases | 502, 526 | | | |
| Chronic bronchitis emphysema, bronchiectasis | 241, 317, 0, 510, 512, 522, | 4.0 | 73.7 | 29.7 |
| Asthma | 525, 527, 583 | 1.5 | 42.4 | 32.6 |
| Other chronic respiratory diseases (excluded pneumoconiosis) | (783.0 excl.) | 1.1 | 20.5 | 17.6 |
| Total | | 6.6 | 45.5 | 26.6 |
| Chronic arthritis and arthrosis | 722–725 | 5.6 | 102.2 | 112.2 |
| Ulcer of stomach and duodenum | 540–542 | 5.0 | 55.5 | 55.6 |
| Displacement of intervertebral disc | 735 | 4.3 | 95.8 | 103.6 |
| *Acute diseases* | | | | |
| Psychoneurotic disorders | 310–314, 317, 5, 318, 354, 780, 6, 790, 791 | 16.8 | 34.4 | 30.3 |
| Respiratory diseases | 051, 470–475, 480–483, 490–493, 500, 501, 511, 783, 0 | 34.4 | 11.8 | 10.0 |
| Gastrointestinal diseases (excl. appendicitis) | 048, 049, 543, 544, 570, 571, 576 | 7.2 | 14.2 | 12.0 |
| Accidents | 742, N800–N999 | 13.7 | 24.6 | 25.9 |

[a] Insured population of Trade Associations.
[b] I.S.C. – International Statistical Classification of Diseases Injuries and Causes of Death.

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| 1963 | | | 1958 | | |
|---|---|---|---|---|---|
| % of total number of days of absence | Average duration per spell of absence (days) | | % of total number of days of absence | Average duration per spell of absence (days) | |
| | M | F | | M | F |
| 7.3 | 152.8 | 145.5 | 6.2 | 138.4 | 125.7 |
| 0.3 | 63.9 | 50.9 | 0.3 | 56.1 | 49.9 |
| 0.3 | 88.7 | 56.5 | 0.2 | 60.3 | 67.0 |
| 2.6 | 113.9 | 92.1 | 2.5 | 106.5 | 92.1 |
| 0.5 | 115.8 | 31.8 | 0.4 | 112.9 | 41.6 |
| 11.0 | 107.0 | 75.4 | 9.6 | 94.8 | 75.3 |
| 4.3 | 75.9 | 30.6 | 3.8 | 58.7 | 23.4 |
| 1.9 | 43.1 | 32.9 | 2.5 | 34.9 | 26.6 |
| 0.9 | 23.0 | 18.5 | 0.9 | 24.6 | 17.0 |
| 7.1 | 47.3 | 27.3 | 7.2 | 39.4 | 22.3 |
| 5.6 | 93.1 | 105.9 | 6.1 | 92.2 | 98.5 |
| 5.0 | 54.5 | 51.6 | 7.2 | 53.6 | 54.2 |
| 4.5 | 83.1 | 97.9 | 5.3 | 79.3 | 94.7 |
| 13.8 | 31.2 | 27.4 | 10.7 | 26.6 | 24.5 |
| 37.5 | 13.1 | 10.4 | 37.8 | 11.7 | 9.9 |
| 7.6 | 14.1 | 11.7 | 6.2 | 13.0 | 11.2 |
| 14.4 | 25.4 | 26.1 | 11.4 | 23.6 | 23.7 |

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Table 2. *Mortality from asthma[a] and chronic bronchitis [b], males and females, per 100 000 of each age group, 1959–1971, the Netherlands*

From: The International Statistical Classification of Diseases, Injuries and Causes of Death.

| Year | Age (years) < 20 | 20–39 |
|---|---|---|
| 1959 | 0.2 | 1.1 |
| 1960 | 0.2 | 1.4 |
| 1961 | 0.2 | 1.0 |
| 1962 | 0.2 | 0.9 |
| 1963 | 0.2 | 1.2 |
| 1964 | 0.2 | 1.1 |
| 1965 | 0.2 | 1.1 |
| 1966 | 0.3 | 0.9 |
| 1967 | 0.3 | 1.7 |
| 1968 | 0.2 | 1.0 |
| 1969 | 0.3 | 1.1 |
| 1970 | 0.1 | 0.4 |
| 1971 | 0.3 | 0.6 |

[a] Number 241 (–1968), 493 (1969+).
[b] Number 491 (–1968), 502 (1969+).

Table 3. *Attendance rate, 1968–1972*

| Year | Attendance popul. A[a] (%) | Attendance popul. B[a] (%) |
|---|---|---|
| 1968 | 70.6 | |
| 1969 | 90.4 | 75.0 |
| 1970 | 92.0 | 85.4 |
| 1971 | 98.2 | 97.5 |
| 1972 | 94.0 | 96.2 |
| All years | 58.3 | 60.0 |

[a] Attendants are equally divided over areas, birth cohorts and sexes.

Table 4. *Number and percentage of positive and negative answers, per question*

| Question (1968) | Hoogvliet, Number 622 Yes | No | Unknown | IJsselmonde, Number 630 Yes | No | Unknown |
|---|---|---|---|---|---|---|
| 3. Did your child cough like this on most days for as much as three or more months a year? | 46 (7) | 573 (92) | 3 | 45 (7) | 584 (93) | 1 |
| 4. Did your child cough like this on most days in winter for as much as three or more consecutive months? | 24 (4) | 595 (96) | 3 | 19 (3) | 611 (97) | |
| 5. Did your child cough like this on most days in summer for as much as three or more consecutive months? | 6 (1) | 613 (99) | 3 | 3 (1) | 627 (99) | |

In parenthesis: in % of total.

Table 5. *Answer to question 36a (1968), 47a (1969). (Did your child ever suffer from eczema), 1968–1969*

| Group | $p$ | $P$ | $\pi$ | Number investigated |
|---|---|---|---|---|
| 1–1[a] | 0.051 | 0.004 | 0.019 | 274 |
| 1–3[b] | 0.025 | 0.004 | 0.060 | 241 |
| 2–1 | 0.084 | 0.005 | 0.033 | 203 |
| 2–3 | 0.087 | 0.027 | 0.034 | 237 |

[a] In 1968 interviewer 1, in 1969 interviewer 1
[b] In 1968 interviewer 1, in 1969 interviewer 3, etc.

Table 6. *Answer to question 36e (1968), 47e (1969). (Have the tonsils been removed), 1968–1969*

| Group | $p$ | $P$ | $\pi$ | Number investigated |
|---|---|---|---|---|
| 1–1[a] | 0.535 | 0.008 | 0.079 | 275 |
| 1–3[b] | 0.569 | 0.004 | 0.107 | 241 |
| 2–1 | 0.598 | 0.000 | 0.049 | 204 |
| 2–3 | 0.524 | 0.013 | 0.064 | 237 |

[a] In 1969 interviewer 1, in 1969 interviewer 1.
[b] In 1968 interviewer 1, in 1969 interviewer 3, etc.

Table 7. *Reproducibility of histamine thresholds (mg/ml), 1968–1970*[a]

| 1968 | 1969 ≤8 | 1969 16 + ≥32 | Total number |
|---|---|---|---|
| ≤8, mg/ml | 6 | 4 | 10 |
| 16 + ≥32, mg/ml | 12 | 184 | 196 |
| Total number | 18 | 188 | 206 |

| 1968 | 1970 ≤8 | 1970 16 + ≥32 | Total number |
|---|---|---|---|
| ≤8, mg/ml | 2 | 8 | 10 |
| 16 + ≥32, mg/ml | 1 | 166 | 167 |
| Total number | 3 | 174 | 177 |

| 1969 | 1970 <8 | 1970 16 + >32 | Total number |
|---|---|---|---|
| <8, mg/ml | 7 | 48 | 55 |
| 16 + >32, mg/ml | 3 | 661 | 664 |
| Total number | 10 | 709 | 719 |

[a] Measurements in May–June of each year.

Table 8. *Number of children investigated, according to birth cohort, sex and symptom group, 1968–1972 (population A)*

Dyspnoea +, Cough +, c + w + n +: see text page 15

| Birth cohort | Sex | Dyspnoea + Cough + | Dyspnoea + Cough − | Dyspnoea − Cough + | Dyspnoea − Cough − c + w + n + | c + w − n + | c + w + n − | c + w − n − | c − w + n + | c − w − n + | c − w + n − | c − w − n − | Unknown | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1968** | | | | | | | | | | | | | | |
| 1/10/60 | M | 6 | 13 | 8 | 6 | 6 | 5 | 5 | 2 | 29 | 4 | 130 | 0 | 214 |
| 30/9/61 | F | 1 | 11 | 9 | 3 | 2 | 0 | 9 | 1 | 22 | 3 | 152 | 1 | 214 |
| Total | | 7 | 24 | 17 | 9 | 8 | 5 | 14 | 3 | 51 | 7 | 282 | 1 | 428 |
| 1/10/55 | M | 2 | 13 | 0 | 1 | 3 | 1 | 2 | 1 | 19 | 2 | 145 | 1 | 190 |
| 30/9/56 | F | 2 | 6 | 4 | 0 | 1 | 2 | 2 | 0 | 18 | 3 | 161 | 0 | 199 |
| Total | | 4 | 19 | 4 | 1 | 4 | 3 | 4 | 1 | 37 | 5 | 306 | 1 | 389 |
| Total general | | 11 | 43 | 21 | 10 | 12 | 8 | 18 | 4 | 88 | 12 | 588 | 2 | 817 |
| In % of total general | | 1.3 | 5.3 | 2.6 | 1.2 | 1.5 | 1.0 | 2.2 | 0.5 | 10.8 | 1.5 | 71.9 | 0.2 | 100 |
| **1969** | | | | | | | | | | | | | | |
| 1/10/60 | M | 2 | 19 | 4 | 2 | 4 | 3 | 4 | 4 | 20 | 10 | 141 | 1 | 214 |
| 30/9/61 | F | 0 | 16 | 4 | 1 | 5 | 1 | 10 | 0 | 23 | 3 | 151 | 0 | 214 |
| Total | | 2 | 35 | 8 | 3 | 9 | 4 | 14 | 4 | 43 | 13 | 292 | 1 | 428 |
| 1/10/55 | M | 2 | 24 | 0 | 0 | 2 | 1 | 2 | 1 | 13 | 4 | 141 | 0 | 190 |
| 30/9/56 | F | 3 | 25 | 0 | 0 | 5 | 0 | 4 | 1 | 15 | 2 | 143 | 1 | 199 |
| Total | | 5 | 49 | 0 | 0 | 7 | 1 | 6 | 2 | 28 | 6 | 284 | 1 | 389 |
| Total general | | 7 | 84 | 8 | 3 | 16 | 5 | 20 | 6 | 71 | 19 | 576 | 2 | 817 |
| In % of total general | | 0.9 | 10.3 | 1.0 | 0.3 | 2.0 | 0.6 | 2.4 | 0.7 | 8.7 | 2.3 | 70.6 | 0.2 | 100 |
| **1970** | | | | | | | | | | | | | | |
| 1/10/60 | M | 3 | 23 | 2 | 2 | 2 | 1 | 4 | 4 | 24 | 6 | 143 | 0 | 214 |
| 30/9/61 | F | 3 | 10 | 1 | 0 | 5 | 2 | 2 | 4 | 24 | 6 | 157 | 0 | 214 |
| Total | | 6 | 33 | 3 | 2 | 7 | 3 | 6 | 8 | 48 | 12 | 300 | 0 | 428 |
| 1/10/55 | M | 3 | 23 | 1 | 1 | 1 | 0 | 7 | 1 | 17 | 5 | 129 | 2 | 190 |
| 30/9/56 | F | 0 | 18 | 0 | 1 | 3 | 0 | 2 | 1 | 20 | 5 | 149 | 0 | 199 |
| Total | | 3 | 41 | 1 | 2 | 4 | 0 | 9 | 2 | 37 | 10 | 278 | 2 | 389 |
| Total general | | 9 | 74 | 4 | 4 | 11 | 3 | 15 | 10 | 85 | 22 | 578 | 2 | 817 |
| In % of total general | | 1.1 | 9.1 | 0.5 | 0.5 | 1.3 | 0.3 | 1.8 | 1.2 | 10.4 | 2.7 | 70.9 | 0.2 | 100 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1971** | | | | | | | | | | | | | | |
| 1/10/60 | M | 5 | 20 | 3 | 1 | 1 | 2 | 5 | 5 | 15 | 7 | 146 | 4 | 214 |
| 30/9/61 | F | 2 | 17 | 1 | 1 | 8 | 3 | 3 | 1 | 13 | 2 | 163 | 0 | 214 |
| Total | | 7 | 37 | 4 | 2 | 9 | 5 | 8 | 6 | 28 | 9 | 309 | 4 | 428 |
| 1/10/55 | M | 1 | 19 | 1 | 1 | 2 | 1 | 3 | 0 | 10 | 5 | 144 | 3 | 190 |
| 30/9/56 | F | 0 | 27 | 1 | 0 | 7 | 1 | 3 | 1 | 12 | 1 | 144 | 2 | 199 |
| Total | | 1 | 46 | 2 | 1 | 9 | 2 | 6 | 1 | 22 | 6 | 288 | 5 | 389 |
| Total general | | 8 | 83 | 6 | 3 | 18 | 7 | 14 | 7 | 50 | 15 | 597 | 9 | 817 |
| In % of total general | | 1.0 | 10.2 | 0.7 | 0.3 | 2.2 | 0.9 | 1.7 | 0.9 | 6.1 | 1.8 | 73.1 | 1.1 | 100 |
| **1972** | | | | | | | | | | | | | | |
| 1/10/60 | M | 3 | 16 | 4 | 1 | 3 | 0 | 1 | 6 | 15 | 9 | 153 | 3 | 214 |
| 30/9/61 | F | 0 | 11 | 3 | 2 | 3 | 0 | 3 | 2 | 17 | 6 | 163 | 4 | 214 |
| Total | | 3 | 27 | 7 | 3 | 6 | 0 | 4 | 8 | 32 | 15 | 316 | 7 | 428 |
| 1/10/55 | M | 2 | 12 | 3 | 0 | 2 | 0 | 2 | 2 | 10 | 8 | 149 | 0 | 190 |
| 30/9/56 | F | 0 | 19 | 2 | 0 | 5 | 1 | 1 | 1 | 15 | 0 | 150 | 5 | 199 |
| Total | | 2 | 31 | 5 | 0 | 7 | 1 | 3 | 3 | 25 | 8 | 299 | 5 | 389 |
| Total general | | 5 | 58 | 12 | 3 | 13 | 1 | 7 | 11 | 57 | 23 | 615 | 12 | 817 |
| In % of total general | | 0.6 | 7.1 | 1.5 | 0.3 | 1.6 | 0.1 | 0.9 | 1.3 | 7.0 | 2.8 | 75.3 | 1.5 | 100 |

Table 9*a*. *Number and percentage of children with cough, breathlessness on exertion, asthmatic attacks, rhinitis, according to birth cohort, 1968–1972 (population A)*

In parenthesis: % of total number. Total numbers differ because of unknown or unreliable answers in some items

| | Birth cohort 1/10/60–30/9/61 | | | | Birth cohort 1/10/55–30/9/56 | | | |
|---|---|---|---|---|---|---|---|---|
| Year | Age | Pos. | Neg. | Total | Age | Pos. | Neg. | Total |
| 1. Cough · 3 months a year[a] | | | | | | | | |
| 1968 | 6/7 | 52 (*12.1*) | 376 | 428 | 11/12 | 17 (*4.3*) | 372 | 389 |
| 1969 | 7/8 | 27 (*6.3*) | 401 | | 12/13 | 8 (*2.0*) | 381 | |
| 1970 | 8/9 | 19 (*4.4*) | 409 | | 13/14 | 12 (*3.0*) | 377 | |
| 1971 | 9/10 | 18 (*4.2*) | 407 | | 14/15 | 11 (*2.8*) | 378 | |
| 1972 | 10/11 | 15 (*3.5*) | 412 | | 15/16 | 14 (*3.6*) | 375 | |
| 2. Cough, ≥3 consecutive months, in winter and/or summer[b] | | | | | | | | |
| 1968 | 6/7 | 24 (*5.6*) | 400 | 424 | 11/12 | 8 (*2.0*) | 375 | 383 |
| 1969 | 7/8 | 9 (*2.1*) | 415 | | 12/13 | 5 (*1.3*) | 378 | |
| 1970 | 8/9 | 9 (*2.1*) | 415 | | 13/14 | 4 (*1.0*) | 379 | |
| 1971 | 9/10 | 11 (*2.6*) | 413 | | 14/15 | 3 (*0.7*) | 380 | |
| 1972 | 10/11 | 10 (*2.3*) | 414 | | 15/16 | 7 (*1.8*) | 375 | |
| 3. Cough, 1 and 2 consecutive months, in winter and/or summer[c] | | | | | | | | |
| | | 1 month | 2 months | | | 1 month | 2 months | |
| 1968 | 6/7 | — | — | — | 11/12 | — | — | — |
| 1969 | 7/8 | 37 (*8.6*) | 19 (*4.4*) | 428 | 12/13 | 17 (*4.3*) | 8 (*2.0*) | 389 |
| 1970 | 8/9 | 30 (*7.0*) | 14 (*3.2*) | | 13/14 | 26 (*6.6*) | 7 (*1.8*) | |
| 1971 | 9/10 | 38 (*8.8*) | 21 (*4.9*) | | 14/15 | 21 (*5.4*) | 7 (*1.8*) | |
| 1972 | 10/11 | 22 (*5.1*) | 11 (*2.5*) | | 15/16 | 19 (*4.8*) | 9 (*2.3*) | |
| 4. Dyspnoea on exertion in winter and/or summer[d] | | | | | | | | |
| | | Pos. | Neg. | | | Pos. | Neg. | |
| 1968 | 6/7 | 17 (*4.0*) | 407 | 424 | 11/12 | 17 (*4.4*) | 368 | 385 |
| 1969 | 7/8 | 36 (*8.4*) | 388 | | 12/13 | 52 (*13.5*) | 333 | |
| 1970 | 8/9 | 38 (*8.9*) | 386 | | 13/14 | 43 (*11.1*) | 342 | |
| 1971 | 9/10 | 45 (*10.6*) | 379 | | 14/15 | 47 (*12.2*) | 338 | |
| 1972 | 10/11 | 27 (*6.3*) | 397 | | 15/16 | 31 (*8.0*) | 354 | |
| 5. Asthmatic attacks, in winter and/or summer[e] | | | | | | | | |
| 1968 | 6/7 | 16 (*3.7*) | 410 | 426 | 11/12 | 12 (*3.1*) | 374 | 386 |
| 1969 | 7/8 | 2 (*0.4*) | 424 | | 12/13 | 7 (*1.8*) | 379 | |
| 1970 | 8/9 | 3 (*0.7*) | 423 | | 13/14 | 5 (*1.3*) | 381 | |

Table 9*a* (*continued*)

| Year | Birth cohort 1/10/60–30/9/61 | | | | Birth cohort 1/10/55–30/9/56 | | | |
|---|---|---|---|---|---|---|---|---|
| | Age | Pos. | Neg. | Total | Age | Pos. | Neg. | Total |
| 1971 | 9/10 | 3 (0.7) | 423 | | 14/15 | 3 (0.7) | 383 | |
| 1972 | 10/11 | 5 (1.1) | 421 | | 15/16 | 1 (0.2) | 385 | |
| 6. Rhinitis, in winter and/or summer[f] | | | | | | | | |
| 1968 | 6/7 | 52 (12.3) | 370 | 422 | 11/12 | 18 (4.6) | 366 | 384 |
| 1969 | 7/8 | 42 (9.9) | 380 | | 12/13 | 17 (4.4) | 367 | |
| 1970 | 8/9 | 41 (9.7) | 381 | | 13/14 | 22 (5.7) | 362 | |
| 1971 | 9/10 | 36 (8.5) | 386 | | 14/15 | 13 (3.4) | 371 | |
| 1972 | 10/11 | 26 (6.1) | 396 | | 15/16 | 23 (5.9) | 361 | |

[a] Affirmative answers to one or more of questions 3 (1968); 5, 7 (1969).
[b] Affirmative answers to one or more of questions 4, 5 (1968); 6, 9 (1969).
[c] Affirmative answers to one or more of questions 7, 8, 10, 11 (1969).
[d] Affirmative answers to one or more of questions 15, 16, 17 (1968); 15, 16, 17, 18, 19, 20 (1969).
[e] Affirmative answers to one or more of questions 24 (1968); 27, 29 (1969).
[f] Affirmative answers to one or more of questions 29 (1968); 34, 38 (1969).

Table 9*b*. *Number and percentage of children in symptom-positive groups, 1968–1972* (*population A*)
In parenthesis: % of total number

| Year | Age (years) | Boys | | | Girls | | | Boys + girls | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Pos.[a] | Neg.[b] | Total | Pos.[a] | Neg.[b] | Total | Pos.[a] | Neg.[b] | Total |
| *Birth cohort 1/10/1960–30/9/1961* | | | | | | | | | | |
| 1968 | 6/7 | 27 (12.6) | 187 | 214 | 21 (9.8) | 193 | 214 | 48 (11.2) | 380 | 428 |
| 1969 | 7/8 | 25 (11.6) | 189 | | 20 (9.3) | 194 | | 45 (10.5) | 383 | |
| 1970 | 8/9 | 28 (13.1) | 186 | | 14 (6.5) | 200 | | 42 (9.8) | 386 | |
| 1971 | 9/10 | 28 (13.1) | 186 | | 20 (9.3) | 194 | | 48 (11.2) | 380 | |
| 1972 | 10/11 | 23 (10.7) | 191 | | 14 (6.5) | 200 | | 37 (8.6) | 391 | |
| *Birth cohort 1/10/1955–30/9/1956* | | | | | | | | | | |
| 1968 | 11/12 | 15 (7.9) | 175 | 190 | 12 (6.0) | 187 | 199 | 27 (6.9) | 362 | 389 |
| 1969 | 12/13 | 26 (13.7) | 164 | | 28 (14.1) | 171 | | 54 (13.9) | 335 | |
| 1970 | 13/14 | 27 (14.2) | 163 | | 18 (9.0) | 181 | | 45 (11.6) | 344 | |
| 1971 | 14/15 | 21 (11.1) | 169 | | 28 (14.1) | 171 | | 49 (12.6) | 340 | |
| 1972 | 15/16 | 17 (8.9) | 173 | | 21 (10.6) | 178 | | 38 (9.8) | 351 | |

[a] D+ C+, D+ C−, D− C+; see text p. 15.
[b] Unknown included.

Table 9*c*. *Percentage of children with cough, breathlessness on exertion, asthmatic attacks, rhinitis, and in symptom positive groups according to age (population A)*

| Age (years) | Cough ≥3 months a year | Cough ≥3 consec. months a year | Cough 2 consec. months a year | Cough 1 consec. month a year | Dyspnoea on exertion | Asthmatic attacks | Rhinitis | D+ C+ D+ C− D− D+* |
|---|---|---|---|---|---|---|---|---|
| 6/7 | 12.1 | 5.6 | — | — | 4.0 | 3.7 | 12.3 | 11.2 |
| 7/8 | 6.3 | 2.1 | 4.4 | 8.6 | 8.4 | 0.4 | 9.9 | 10.5 |
| 8/9 | 4.4 | 2.1 | 3.2 | 7.0 | 8.9 | 0.7 | 9.7 | 9.8 |
| 9/10 | 4.2 | 2.5 | 4.9 | 8.8 | 10.6 | 0.7 | 8.5 | 11.2 |
| 10/11 | 3.5 | 2.3 | 2.5 | 5.1 | 6.3 | 1.1 | 6.1 | 8.6 |
| 11/12 | 4.3 | 2.0 | — | — | 4.4 | 3.1 | 4.6 | 6.9 |
| 12/13 | 2.0 | 1.3 | 2.0 | 4.3 | 13.5 | 1.8 | 4.4 | 13.9 |
| 13/14 | 3.0 | 1.0 | 1.8 | 6.6 | 11.1 | 1.3 | 5.7 | 11.6 |
| 14/15 | 2.8 | 0.7 | 1.8 | 5.4 | 12.2 | 0.7 | 3.4 | 12.6 |
| 15/16 | 3.6 | 1.8 | 2.3 | 4.8 | 8.0 | 0.2 | 5.9 | 9.8 |
| Number 6/11 | 428 | 428 | 428 | 428 | 424 | 426 | 422 | 428 |
| Number 11/16 | 389 | 389 | 389 | 389 | 385 | 386 | 384 | 389 |
| Total number all ages | 817 | 817 | 817 | 817 | 809 | 812 | 806 | 817 |

* See text p. 15.

Table 10*a*. *Number and percentage of children, according to the number of years with a positive item, per item and birth cohort (population A)*

In parenthesis: % of total number. Total numbers differ because of unknown or unreliable answers in some items.

| Number of years positive | Cough* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Birth cohort 1/10/60–30/9/61 | | | | Birth cohort 1/10/55–30/9/56 | | | |
| | ≥3 months a year | ≥3 consec. months a year | 2 consec. months a year | 1 consec. month a year | ≥3 months a year | ≥3 consec. months a year | 2 consec. months a year | 1 consec. month a year |
| 0 | 344 (80.3) | 381 (89.0) | 405 (94.6) | 374 (87.4) | 346 (88.9) | 370 (95.1) | 377 (96.9) | 345 (88.6) |
| 1 | 54 (12.6) | 33 (7.7) | 21 (4.9) | 49 (11.4) | 31 (7.9) | 14 (3.6) | 12 (3.0) | 38 (9.7) |
| 2 | 17 (3.9) | 12 (2.8) | 2 (0.4) | 2 (0.4) | 7 (1.8) | 4 (1.0) | 0 | 5 (1.3) |
| 3 | 10 (2.3) | 1 (0.2) | 0 | 3 (0.7) | 4 (1.0) | 0 | 0 | 0 |
| 4 | 2 (0.4) | 1 (0.2) | 0 | 0 | 0 | 0 | 0 | 1 (0.2) |
| 5 | 1 (0.2) | 0 | | | 1 (0.2) | 1 (0.2) | | |
| Total number | 428 | 428 | 428 | 428 | 389 | 389 | 389 | 389 |

* Criteria see Table 9*a*.

Table 10*b*. *Number and percentage of children according to number of years with symptoms,*[a] *birth cohort and sex (population A)*

| Number of years positive | Birth cohort 1/10/60–30/9/61 | | | | | | Birth cohort 1/10/55–30/9/56 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Boys | | Girls | | Boys + girls | | Boys | | Girls | | Boys + girls | |
| | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % |
| 0 | 154 | 71.9 | 167 | 78.0 | 321 | 75.0 | 146 | 76.8 | 150 | 75.4 | 296 | 76.1 |
| 1 | 30 | 14.0 | 23 | 10.7 | 53 | 12.4 | 17 | 8.9 | 20 | 10.0 | 37 | 9.5 |
| 2 | 9 | 4.2 | 13 | 6.1 | 22 | 5.1 | 8 | 4.2 | 14 | 7.0 | 22 | 5.6 |
| 3 | 8 | 3.7 | 5 | 2.3 | 13 | 3.0 | 8 | 4.2 | 3 | 1.5 | 11 | 2.8 |
| 4 | 6 | 2.8 | 5 | 2.3 | 11 | 2.6 | 6 | 3.2 | 10 | 5.0 | 16 | 4.1 |
| 5 | 7 | 3.3 | 1 | 0.5 | 8 | 1.9 | 5 | 2.6 | 2 | 1.0 | 7 | 1.8 |
| Total | 214 | 100 | 214 | 100 | 428 | 100 | 190 | 100 | 199 | 100 | 389 | 100 |

[a] D+ C+, D+ C−, D− C+: see text p. 15.

| Dyspnoea on exertion[a] | | Asthmatic attacks[a] | | Rhinitis[a] | |
|---|---|---|---|---|---|
| Birth cohort | | Birth cohort | | Birth cohort | |
| 1/10/60–30/9/61 | 1/10/55–30/9/56 | 1/10/60–30/9/61 | 1/10/55–30/9/56 | 1/10/60–30/9/61 | 1/10/55–30/9/56 |
| 344 | 300 | 401 | 371 | 330 | 329 |
| *(81.1)* | *(77.9)* | *(94.1)* | *(96.1)* | *(78.2)* | *(85.6)* |
| 39 | 34 | 23 | 10 | 39 | 36 |
| *(9.2)* | *(8.8)* | *(5.4)* | *(2.6)* | *(9.2)* | *(9.3)* |
| 17 | 20 | 1 | 1 | 23 | 8 |
| *(4.0)* | *(5.2)* | *(0.2)* | *(0.2)* | *(5.4)* | *(2.0)* |
| 10 | 13 | 0 | 1 | 16 | 5 |
| *(2.3)* | *(3.3)* | | *(0.2)* | *(3.8)* | *(1.3)* |
| 10 | 13 | 1 | 2 | 6 | 4 |
| *(2.3)* | *(3.3)* | *(0.2)* | *(0.4)* | *(1.4)* | *(1.0)* |
| 4 | 5 | 0 | 1 | 8 | 2 |
| *(0.9)* | *(1.3)* | | *(0.2)* | *(1.9)* | *(0.5)* |
| 424 | 385 | 426 | 386 | 422 | 384 |

[a] *Criteria see Table 9a.*

Table 11. *Number and percentage of children according to symptoms and previous history (population A)*

| Positive answer on question* | | Cough >3 months a year | | | | Cough ≥3 consecutive months a year | | | | Cough 2 consecutive months a year | | | | Cough 1 consecutive months a year | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1–5 × | | 0 × | | 1–5 × | | 0 × | | 1–4 × | | 0 × | | 1–4 × | | 0 × | |
| | | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % | *N* | % |
| 36*h* ('68) | 178 | 62 | 48.8 | 116 | 16.7 | 37 | 56.1 | 141 | 18.8 | 14 | 40.0 | 164 | 21.0 | 44 | 44.9 | 134 | 18.7 |
| 36*i* ('68) | 308 | 103 | 81.1 | 205 | 29.8 | 58 | 87.8 | 250 | 33.4 | 23 | 65.7 | 285 | 36.5 | 56 | 57.1 | 252 | 35.1 |
| 36*j* ('68) | 83 | 21 | 16.5 | 62 | 9.0 | 11 | 16.7 | 72 | 9.6 | 5 | 14.2 | 78 | 10.0 | 20 | 20.4 | 63 | 8.8 |
| 19 ('68) | 206 | 65 | 51.2 | 141 | 20.5 | 38 | 57.6 | 168 | 22.4 | 17 | 48.6 | 189 | 24.2 | 39 | 39.8 | 167 | 23.3 |
| 12 ('69) | 138 | 61 | 48.0 | 77 | 11.2 | 37 | 56.1 | 101 | 13.5 | 14 | 40.0 | 124 | 15.9 | 34 | 34.7 | 104 | 14.5 |
| 21 ('69) | 115 | 47 | 37.0 | 68 | 9.9 | 33 | 50.0 | 82 | 10.9 | 10 | 28.6 | 105 | 13.5 | 27 | 27.6 | 88 | 12.3 |
| 28 ('69) | 27 | 14 | 11.0 | 13 | 1.9 | 8 | 12.1 | 19 | 2.5 | 3 | 8.6 | 24 | 3.1 | 8 | 8.2 | 19 | 2.6 |
| 30 ('69) | 22 | 11 | 1.6 | 7 | 10.6 | 15 | 2.0 | 3 | 8.6 | 19 | 2.4 | 6 | 6.1 | 16 | 2.2 | 16 | 2.2 |
| Total number | 815 | 127 | | 688 | | 66 | | 749 | | 35 | | 780 | | 98 | | 217 | |

* 36*h* (1968) Did your child ever have periods of asthma or bronchitis?
36*i* (1968) Did your child ever have periods of cough?
36*j* (1968) Did your child ever have pneumonia?
19 (1968) Did your child ever wheeze?
12 (1969) Did your child ever have periods of cough for as much as 3 consecutive months in the previous years?
21 (1969) Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase in the previous years?
28 (1969) When resting did your child ever have attacks with shortness of breath in winter in the previous years?
30 (1969) When resting did your child ever have attacks with shortness of breath in summer in the previous years?

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SUMMARY: Asthma, chronic bronchitis and emphysema (chronic nonspecific respiratory disease, CNSRD) are common conditions in adults (32,34) and children (29) in the Netherlands. Many children with symptoms belonging to the CNSRD syndrome will continue to have these into adult life[1] (3,9,17,21,23,42,44,53,54). The various studies concerning the history of CNSRD in childhood are hardly comparable as regards their design and results. The definitions of asthma, asthmatic bronchitis, recurrent bronchitis and chronic bronchitis in children and the criteria for recovery or improvement are not sufficiently clear. Recent and previous symptoms are often not differentiated. The critical evaluation of the effect of treatment on the course of the disease is insufficient in most studies.

In the majority of children , the symptoms of CNSRD begin in the first five years of life. The chance that they will persist into adulthood seems to be least in those children, in whom symptoms are not frequent or slight and disappear during school age. Some findings suggest that optimum treatment and favourable psychosocial conditions have a beneficial effect on the course of the disease. However, to quantitate these is difficult.

It will therefore often be impossible to make a reasonable prediction of the prognosis of CNSRD in childhood for adult life. In order to ensure optimum curative and preventive medical care, it will be essential to examine the conditions in which the injurious effects of exogenous factors, such as allergens, infections, chemical and physical agents and unfavourable psychosocial circumstances, are reduced to a minimum. However, studies on the relative significance of various exogenous factors are difficult to perform. These studies are merely practicable in homogeneous, clearly defined populations living under specific conditions in which only a limited number of exogenous factors play a role.

In view of the morbidity of CNSRD, the most extensive possible preventive care in addition to optimum treatment of signs and symptoms is essential. Among others, this will include counselling of smokers, vocational guidance, advice on housing, etc. This is of importance in adults and, to an even greater extent, in subjects in the 10-20 year range, in whom adequate health care and health counselling will contribute to a favourable course.

In adults morbidity and absenteeism due to CNSRD would presumably be considerably reduced if children running and increased risk of CNSRD in later life could be selected at an early stage and given adequate care.

This aspect, i.e. the selection of children running an increased risk, is the subject of the present study.

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SUPPLEMENT 261, 1977

# CHRONIC NONSPECIFIC RESPIRATORY DISEASE IN CHILDREN, A FIVE YEAR FOLLOW-UP STUDY

BY

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CONTENTS



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## 1. INTRODUCTION

Asthma, chronic bronchitis and emphysema (chronic nonspecific respiratory disease, CNSRD) are common conditions in adults (32, 34) and children (29) in the Netherlands. Many children with symptoms belonging to the CNSRD syndrome will continue to have these into adult life[1] (3, 9, 17, 21, 23, 42, 44, 53, 54). The various studies concerning the history of CNSRD in childhood are hardly comparable as regards their design and results. The definitions of asthma, asthmatic bronchitis, recurrent bronchitis and chronic bronchitis in children and the criteria for recovery or improvement are not sufficiently clear. Recent and previous symptoms are often not differentiated. The critical evaluation of the effect of treatment on the course of the disease is insufficient in most studies.

In the majority of children, the symptoms of CNSRD begin in the first five years of life. The chance that they will persist into adulthood seems to be least in those children, in whom symptoms are not frequent or slight and disappear during school age. Some findings suggest that optimum treatment and favourable psychosocial conditions have a beneficial effect on the course of the disease. However, to quantitate these is difficult.

It will therefore often be impossible to make a reasonable prediction of the prognosis of CNSRD in childhood for adult life. In order to ensure optimum curative and preventive medical care, it will be essential to examine the conditions in which the injurious effects of exogenous factors, such as allergens, infections, chemical and physical agents and unfavourable psychosocial circumstances, ar reduced to a minimum. However, studies on the relative significance of various exogenous factors are difficult to perform. These studies are merely practicable in homogeneous, clearly defined populations living under specific conditions in which only a limited number of exogenous factors play a role.

In view of the morbidity of CNSRD, the most extensive possible preventive care in addition to optimum treatment of signs and symptoms is essential. Among others, this will include counselling of smokers, vocational guidance, advice on housing, etc. This is of importance in adults and, to an even greater extent, in subjects in the 10–20 year range, in whom adequate health care and health counselling will contribute to a favourable course.

In adults morbidity and absenteeism due to CNSRD would presumably be considerably reduced if children running and increased risk of CNSRD in later life could be selected at an early stage and given adequate care.

This aspect, i.e. the selection of children running an increased risk, is the subject of the present study.

## 2. EPIDEMIOLOGY OF CNSRD

### 2.1. PREVALENCE

For the literature on the prevalence of CNSRD in the Netherlands and other countries, the reader is referred to the thesis by Van der Lende (31) and a number of papers published by the TNO Working group on the Epidemiology of CNSRD (33, 34).

[1] A detailed review of this literature is available at the author.

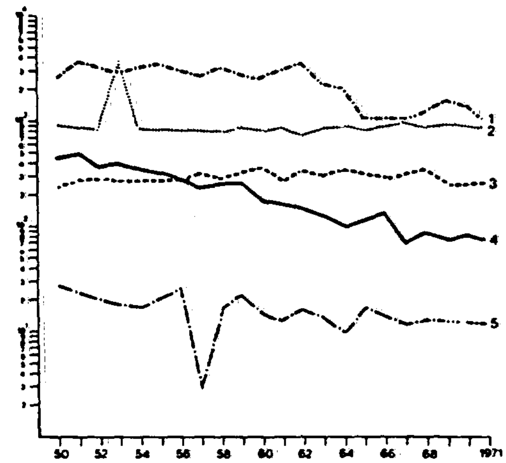


*Fig. 1.* Deaths by congenital malformations (1) (numbers 750–759 (– '68), 740–759 ('69 – )), accidents (2) (numbers E800–E999), neoplasms (3) (numbers 140–239), pneumonia (4) (numbers 490–493 (– '68), 480–486 ('69 + 1)), and chronic non specific lung diseases (5) (numbers 241, 502, 526, 527.1 (– '68), 493, 391, 518, 492 ('69 + ), boys and girls, 0–14 years of age, 1950–1971, The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

## 2.2. ABSENTEEISM DUE TO SICKNESS

Table 1 shows absenteeism due to a number of chronic and acute conditions in the Netherlands in 1958, 1963 and 1966. More recent data have not been published.

Among the chronic conditions, chronic respiratory disease (mainly CNSRD) is the next important cause of absenteeism after cardiovascular disease. Absenteeism was estimated at from 10 000 to 11 000 man years in 1966.

The considerable social significance of acute respiratory conditions which cause five times the absenteeism due to chronic respiratory disease is accentuated by the table. It should be pointed out that it is not impossible but even likely that part of the absenteeism resulting from acute respiratory conditions occurs in cases of chronic respiratory disease and is directly due to the latter. The figures reported for chronic respiratory disease as the cause of absenteeism are therefore likely to be minimum figures.

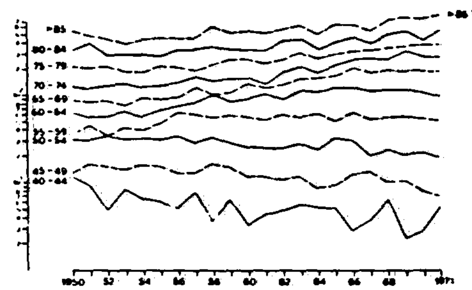


*Fig. 2.* Mortality from chronic nonspecific lung diseases (numbers 241, 502, 526, 527.1) (– '68), 493, 491, 518, 492 ('69 + )), males, per 100 000 of each age group, 1950–1971, The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

## 2.3. MORTALITY

In 1968, Speizer (47) and his associates published mortality rates from asthma in a number of countries. These showed a marked increase in subjects in the 10–19 year range in Great Britain, Japan and Australia. It was suggested that this could have been due to the excessive use of aerosol bronchodilators and the fact that administration of steroids during exacerbations was inadequate.

Table 2 shows the death rates from asthma and chronic bronchitis in subjects in the 0–39 year range per 100 000 of each age group in the Netherlands. The rates are very low and there was no increase during the period from 1959 to 1971.

The difference in mortality rates between the

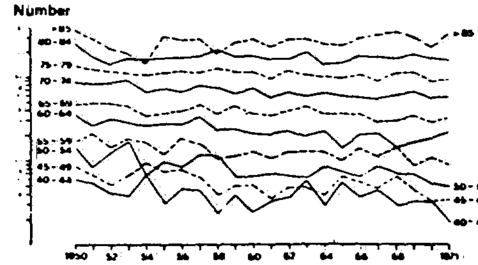


*Fig. 3.* Mortality from chronic nonspecific lung diseases (numbers 241, 502, 526, 527.1 (– '68), 493, 491, 518, 492 ('69 + )), females, per 100 000 of each age group, 1950–1971, The Netherlands. International statistical classification of diseases, injuries and causes of death.

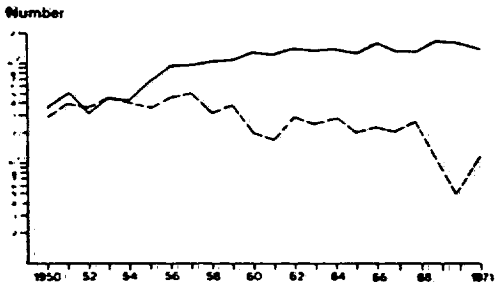


*Fig. 4.* Deaths by chronic bronchitis and emphysema, —, (numbers 502 + 527.1 (– '68) 491 + 492 ('69 –)) and asthma, – – –, (numbers 241 (– '68), 493 ('69 –)), males, 55–59 years of age, 1950–1971, The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

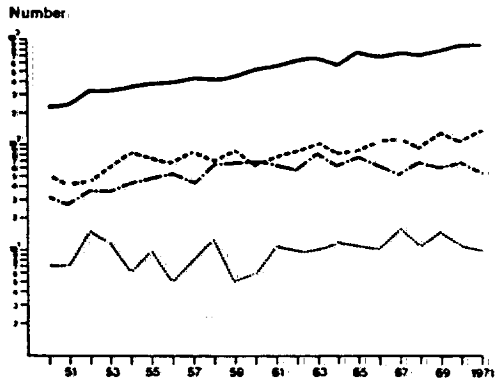


*Fig. 5.* Mortality from chronic bronchitis and emphysema (numbers 502 resp. 527.1 (– '68), 491 resp. 492 ('69 – )) compared to mortality from arteriosclerotic heart disease (numbers 420 (– '68), 410, 411, 412, 413, 414 ('69 –)), men (—– —) and women (--- —), 50–54 years of age, The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

Netherlands and Great Britain is hard to account for, particularly as the clinical picture and general schedules of treatment are comparable in the two countries.

In Figure 1, the number of subjects in the 0–14 year range who died from CNSRD is compared with the number of deaths from congenital malformations, accidents, neoplasms and pneumonia. These figures also show that CNSRD is a minor cause of death in children.

Figures 2 and 3 show the mortality from CNSRD per 100 000 men and women over forty. Mortality is higher in men than it is in women. The men show an increase from the 55th year of life. This begins about the year 1954. The increase is caused by chronic bronchitis and emphysema, as is apparent from Figure 4. (This figure is concerned with subjects in the 55–59 year range; it also holds true, however, for the older age groups.) The cause of this increase is obscure. Increased cigarette smoking may possibly be a factor. An outstanding feature is the fact that the mortality from bronchitis and emphysema runs parallel to that from cardiovascular disease, although absolute mortality is lower. This is illustrated in Figure 5 for those in the 50–54 year range.

## 3. STUDY DESIGN AND OBJECTIVES

From 1968–1972 a follow-up study on symptoms and signs of CNSRD was performed in randomly selected populations of schoolchildren in Rotterdam.

The aim was to investigate the appearance or disappearance of symptoms of CNSRD and to select children running an increased risk of CNSRD in adult life by means of a standardised questionnaire. This was supplemented by pulmonary function tests, determination of the bronchial reactivity, allergy skin tests, chest radiography and investigations about social factors, air pollution, parental smoking habits and parental respiratory symptoms.

## 4. POPULATIONS STUDIED

4.1. In 1968, this consisted of:

(1) 175 boys and 175 girls born during the period from October 1960 to October 1961 and living in the Hoogvliet district.

(2) 175 boys and 175 girls born during the period from October 1955 to October 1956 and living in the Hoogvliet district.

(3) 175 boys and 175 girls born during the period from October 1960 to October 1961 and living in the IJsselmonde district.

(4) 175 boys and 175 girls born during the period from October 1955 to October 1956 and living in the IJsselmonde district.

The total number was 700 children of Hoogvliet and 700 children of IJsselmonde. *This population will henceforth be referred to as population A*. These were randomly selected populations taken from children born during the above periods and living in Hoogvliet and IJsselmonde on October 1, 1967. They were chosen for the following reasons:

(1) Clinical experience has shown that changes in the occurrence of symptoms of CNSRD can be expected in the 6–16 year range.

(2) The two districts are newly constructed areas with favourable housing and social conditions.

(3) Industrial air pollution was greater in the Hoogvliet district than it was in the IJsselmonde district at the beginning of the study.

4.2. As it was advisable to increase the number of children with symptoms in view of the follow-up, 255 children of the relevant cohorts, who were recorded as having symptoms of CNSRD by the school medical officers and living in Hoogvliet and IJsselmonde, were selected in 1969. The findings in these children were used only in longitudinal studies and not in data on prevalence. *This population will be further referred to as population B.*

4.3. The numbers and proportions of children of populations A and B who fully took part in the study during the period from 1968 to 1972 are listed in Table 3. In each year, the children are equally distributed over the districts and sexes; the number of those of the older cohort taking part is slightly smaller than is that of those of the younger cohort. (The difference was approximately 10 per cent in 1972.) The reasons for not taking part were traced wherever possible by home visits or telephone calls. Although specific inquiries were made in this regard, respiratory symptoms were not stated as the reason in any of these cases. Change of residence was the reason in approximately one-third of those who did not take part in the study during the period from 1969 to 1972; the other most often stated reasons were:

— objections to committing oneself to a five-year period
— objections on schoolabsence
— objections on principle
— inadequate interest in the study
— family reasons
— severe mental or physical disorders in the child to be studied
— refusal on the part of the child.

## 5. METHODS OF INVESTIGATION

### 5.1. QUESTIONNAIRES ON SYMPTOMS

#### 5.1.1. *General*

A European Coal and Steel Community (ECSC) questionnaire modified for children was used in taking the medical histories of the children. In 1968, the histories concerned the last two years; in the next few years, they only concerned the year just ended. The questions were asked by two investigators (physicians). In 1968,

the parents were sent a questionnaire in advance with the request to complete it at home. The questions asked in the questionnaire were broadly similar to those asked during the investigation. This self-administered questionnaire was designed to prepare the parents for the questions that would be asked during the investigation. It was regarded as essential that the answers should reflect reality wherever possible, i.e., that the methods adopted in this study should discriminate as sharply as possible. For this reason, the original ECSC questionnaire was modified to some extent as early as 1968. Specifically the following passage was included orally in questions 1–3 after "usually": "that is to say, as many as five days a week on average". Moreover questions 4 and 5 were added, in which it was explicitly stated what was meant by "three months a year", namely, three *consecutive* months a year. Table 4 shows that this makes a considerable difference in the number of affirmative answers. The questionnaire was extended with questions on cough for two months and one month in 1969. Therefore the numbering of the questions had to be changed in 1969. It is already indicated in the text and the tables to which year the numbering of a question refers. The questionnaire is given in Appendix 1.

### 5.1.2. *Reliability of the questionnaire*

(1) The answers to question 36 *h* (1968) ("Did your child ever have any attacks of bronchitis or asthma?") were compared with those to questions on cough, dyspnoea and asthmatic attacks. All children examined were classified into one of four symptom groups (dyspnoea + cough + (D + C +) dyspnoea + cough − (D + C −) dyspnoea − cough + (D − C +) dyspnoea − cough − (D − C −). For details, see Section 6.1, p. 15).

This comparison did not justify any doubt as to the correctness of the answers to the questions used in classifying the children into symptom groups.

(2) It was checked whether children showing symptoms of CNSRD which were severe enough for referral to the outpatient department of the respiratory unit of the Sophia Children's Hospital, always were classified into one of the symptom-positive groups after their parents had answered the questionnaire. This was done in 76 children. Independently another investigator attempted to answer the questionnaire using the children's hospital records.

The difference between and similarity of the answers to each question in the records and questionnaire have been recorded.

Fifty-nine percent of the answers were identical in the records and questionnaire, whereas this was not the case with twenty-seven percent. Fourteen percent of the answers were not reliable.

The similarity was found to be most marked in questions relating to the previous histories of the subjects. In view of the background of the children, this is an obvious finding.

Cough was less frequently coded in the affirmative according to the questionnaire than it was according to the records. The similarity of the questions on dyspnoea was fairly close.

*Conclusion.* In the children showing respiratory symptoms, there is inadequate similarity between the findings in the questionnaire and those in the records as regards the symptom cough and fairly adequate similarity where the symptom dyspnoea is concerned. The questionnaire shows an underreporting of the symptom cough.

(3) A number of the variables included in the study, such as cough and dysponoea, are marked by dichotomy of the values, i.e., they show whether a particular symptom has or has not occurred or whether it is present.

Efforts were made to study the variations in frequency distribution of such a variable from one survey to another. The following parameters were introduced for this purpose.

$p$ = possibility in errors of coding
$P$ = possibility of appearance of the symptom with which the question is concerned at the time of the first survey

$\pi$ = possibility of the symptom having occurred during the interval between the first and second surveys.

The values of $p$, $P$ and $\pi$ about the variables "history of eczema" (question 47*a* (1969)) and "tonsils removed" (question 36*e* (1968)) have been estimated by the maximum likelihood method. This was done separately in four groups. These groups differed from one another in that they were questioned by different interviewers in at least one of the two years during which inquiries were conducted. These questions are best suited to verify the reproducibility of the result obtained, as a finding which was positive in 1968 should continue to be so during the following years. The calculated estimates of the values of $p$, $P$ and $\pi$ are shown in Tables 5 and 6. The groups in these tables are composed according to the numbers of the successive interviewers; group 1–3 for instance, includes those children who were interviewed by interviewer 1 in 1968 and interviewer 3 in 1969.[1]

The tables show that the estimated value of $p$ (the percentage of faulty codings) continues to be very low. It is highest in group 2–3.

(4) In fifty children of the oldest birth cohort, the questionnaires were separately submitted to the mother and the child at several weeks' intervals. The similarity between the answers given on the two occasions ranged from good to excellent.

(5) As is apparent from Tables 12 and 13, the mean one-second forced expiratory volume ($FEV_{1.0}$) and the mean forced expiratory volume expressed as a percentage of the vital capacity ($FEV_{1.0}\%$) of children with dyspnoea on exertion are significantly lower than those in children showing no respiratory symptoms (D- C-, c w n ) (for further explanation of these tables, see p. 18).

*Conclusion drawn from studies on the reliability of the questionnaire.* The answers to the questions asked in the questionnaire appear to be fairly reliable and readily reproducible. Appreciable differences between interviewers were not observed. Comparison of the results obtained using the questionnaire with the findings in the records of the out-patient department is not possible. A small proportion of the out-patients to whom the questions of the questionnaire were put were classified with the group in which symptoms were absent. This was probably due to the fact that treatment had reduced the symptoms to such an extent in these cases that they no longer satisfied the criteria adopted for the groups in which symptoms were present. This may, naturally, also be the case in population surveys and may result in an unduly low symptom prevalence rate. The symptom most difficult to evaluate is dyspnoea on exertion. The $FEV_{1.0}\%$ of children who showed only this symptom is significantly lower than that in nondyspnoeic subjects, which supports the reliability of the indicative value of this question. Appendix II includes a review of the literature on observer's errors.

## 5.2. SOCIAL QUESTIONNAIRE

In 1969 and 1970, the homes of all children who had taken part in the entire survey in 1969 were visited. A questionnaire on social and demographic data was completed by a health visitor trained for this work. If required, she explained the purpose of the survey in greater detail and also urged people to continue taking part in it to the best of their ability. This data was collected for the purpose of obtaining information on the social and demographic backgrounds of the children under investigation and their families.

## 5.3. QUESTIONNAIRE ON THE STATE OF HEALTH OF PARENTS, BROTHERS AND SISTERS

In 1972, the parents were sent a questionnaire for the purpose of collecting data on the family background of respiratory symptoms and smoking habits (36).

[1] In 1969, interviewer 3 took the place of interviewer 2 who had to discontinue her activities because of change of residence.

## 5.4. PHYSICAL EXAMINATION

The upper and lower respiratory tract were physically examined each year. In addition, the height, weight and physical development were measured by standardized methods (39, 48).

## 5.5. FUNCTION TESTS

Pulmonary function tests were performed and the histamine threshold was determined each year. This was done in population A from 1968 in the oldest and from 1969 in the youngest cohort and in population B from 1969. Pulmonary function tests were invariably performed between the end of April and mid-June to avoid accidental diminution because of respiratory symptoms due to seasonal factors as much as possible. They were only performed when no respiratory symptoms were present at the time of investigation.

### 5.5.1. *Pulmonary function tests*

The following values were determined:

(1) In all children the vital capacity (VC) and one-second forced expiratory volume ($FEV_{1.0}$) using a Lode water sealed spirometer (model D53).

(2) In a limited number of randomly selected children of each birth cohort, the total lung capacity and the residual volume by means of the He method, using a volumograph no. 4 (Mijnhardt).

### 5.5.2. *Histamine threshold*

The reactivity of the bronchi was determined by the histamine threshold (52) using the expiratory peak flow instead of the VC and $FEV_1$ as parameters of bronchial obstruction. The expiratory peak flow was measured with a Wright peak-flow meter.

5.5.2.1. *Comparison of the histamine threshold as measured with the spirometer and with the Wright peak-flow meter.* In 327 children (those taking part in the population survey as well as children attending the out-patient department of the respiratory unit of the Sophia Children's Hospital), the histamine threshold was determined by the spirometer and by the Wright peak-flow meter. The results of the two methods of determination were in good agreement.

5.5.2.2. *Reproducibility of the histamine threshold.* In Table 7, the number of children of population A in whom various determinations of the histamine threshold were carried out during the period from 1968 to 1970 are listed. Normal or slightly lowered histamine thresholds ($16 + \geq 32$ mg/ml) are readily reproducible; markedly lowered thresholds ($\leq 8$ mg/ml) often show an improvement.

5.5.2.3. *Relationship between initial pulmonary function and histamine thresholds.* This was studied in a separate survey (Appendix III). This study showed that there is some relationship between the initial $FEV_{1.0}$ or the peak flow and the histamine threshold. When the histamine threshold is known, however, it is not possible to even approximately predict the $FEV_{1.0}$, nor can the histamine threshold be predicted when the $FEV_{1.0}$ is given. Repeated measurements of pulmonary function and the histamine threshold showed that these often show an opposite trend (i.e. histamine threshold decreases and pulmonary function increases or vice versa).

*Conclusion.* The determination of the histamine threshold as a parameter of the bronchial reactivity seems to be useful in addition to the measurement of the pulmonary function. These two quantities are probably largely determined by different factors. The histamine threshold is readily reproducible in the normal and slightly lowered range when it is measured over a number of years. It would be of major importance to know whether a histamine threshold which is permanently lowered (i.e., also during an optimum clinical period in which the VC and $FEV_{1.0}$ are within normal limits) his any significance for the prognosis.

## 5.6. ALLERGY TESTS

Tests for cutaneous allergy to house dust, mixed moulds,[1] grass pollen[2] and danders[3] were

[1] *The mixed moulds included:* Trichoderma viride, Fusarium culmorum, Cladosporium, Cladosporiades, Cladosporium clatum, Cladosporium herbarum, Rhizo-

performed in population A in 1968 and in population B in 1969. Testing with house dust, grass pollen and danders could be repeated in a number of children in the spring of 1973 after the main study had been completed, by the same technicians.

The allergens used were Diephuis allergens at the following concentrations: intracutaneous injection of 0.5 mg/ml of house dust and, in the case of a positive reaction, additional injection of 0.05 mg/ml and 0.005 mg/ml; intracutaneous injection of 0.2 mg/ml of mixed moulds and when a positive response was obtained, additional injection of 0.02 mg/ml and 0.002 mg/ml; intracutaneous injections of 1 000 Noon units of grass pollen and, for positive reactors, additional injection of 100 Noon units and 10 Noon units; intracutaneous injection of 0.25 mg/ml of danders and, in the event of a positive response, additional injection of 0.025 mg/ml and 0.0025 mg/ml.

The allergens used in 1973 were of the same batch as those used during previous years. They had been stored in the freeze-dried state.

pus nigricans, Stemphylium botryosum, Alternaria tenuis, Penicillium brevi compactum, P. expansum, P. notatum, P. frequentans, P. commune, Aspergillus versicolor, Aspergillus niger, Aspergillus fumigatus, Mucor sponosus, Mucor mucedo, Mucor racemosus, Pullularia pullulans, Botrytis cenerea, Merculius domesticus, Epicoccum purparascens.

[2] *The grass pollen included:* Secale cereale (rye), Dactylis glomerata (cocksfoot grass), Lolium perenne (rye-grass), Anthoxantum odoratum (sweet vernal grass), Alopecurus pratensis (meadow foxtail grass), Agrostis alba (white bent), Holcus lanatus (Yorkshire fog), Cynosurus cristatus (crested dogtail).

[3] *Human and animal danders:* Man, horse, swine, cat, goat, cattle, rabbit,dog, sheep and various birds.

To study the repeatability of the tests for cutaneous allergy in individuals showing a positive response, skin testing was repeated in a number of asthmatic patients of the Sophia Children's Hospital with positive intracutaneous reactions. These patients were treated but had not been desensitized. The technicians performing the skin tests were not aware of the results of the previous tests. The repeatability was, on the whole, highly satisfactory in those age groups in which the present study was carried out.

## 5.7. RADIOGRAPHY

### 5.7.1. *Radiography of the lungs*

In 1968, X-rays of the lungs were made in all children of population A and, in 1969, in all those who were studied in population B. These X-rays were read by H. A. van Geuns, M.D., without knowing the children or their medical histories. He used a standardized method in which particular attention was paid to the lung pattern and hili.

### 5.7.2. *Determination of bone age*

X-rays of the left hand of all children were taken each year to determine the bone age in order to correlate this with height growth, development of puberty and pulmonary function. In each case, the bone age was determined by the same investigator (H.H.−S) using Tanner's method (49).

# 6. RESULTS

## 6.1. CLASSIFICATION INTO SYMPTOM GROUPS

For a convenient arrangement of the results, the following classification into symptom groups was made. It was based on the *major symptoms* of CNSRD i.e. prolonged cough, dyspnoea on exertion and attacks of asthma (Text-table 1).

A classification into four symptom groups was based on the scheme: D+C+, D+C−, D−C+ and D C−.

In the rating dyspnoea +, questions 15 and 24 of 1968 and questions 15, 18, 27 and 29 of

Text-table 1. *Classification into symptom groups based on major symptoms*

| Dyspnoea | Questions 24 (1968), 27 and/or 29 (1969): When resting did your child ever have attacks of shortness of breath with wheezing at rest (asthmatic attacks)? | Questions 15 (1968), 15 and/or 18 (1969): Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase? |
|---|---|---|
| D+ | Yes | Yes |
| | Yes | No |
| | No | Yes |
| D− | No | No |
| **Cough** | **Question 4 (1968) Question 6 (1969) Did your child cough like this[a] on most days in winter for as much as three or more consecutive months?** | **Question 5 (1968) Question 9 (1969) Did your child cough like this[a] on most days in summer for as much as three or more consecutive months?** |
| C+ | Yes | Yes |
| | Yes | No |
| | No | Yes |
| C− | No | No |

[a] i.e. continuously, that is on average 5 days a week.

1969 were combined, as it is difficult to adequately differentiate between dyspnoea on exertion and dyspnoea at rest in children.

The D–C-group was subdivided into on the basis of "secondary" symptoms (Text-table 2).

## 6.2. PREVALENCE OF COUGH, DYSPNOEA ON EXERTION, ASTHMATIC ATTACKS AND RHINITIS IN POPULATION A

Table 8 includes a summary for each year of investigation, based on the birth cohort and sex per symptom group. In Table 9*a*, the number and percentage of children according to the year of investigation and the age of the children are listed for each symptom and birth cohort.

In Table 9*b*, this was done for the combination of symptom-positive groups (D+C+, D+C−, D−C+) per birth cohort and sex. The percentages listed in Tables 9*a* and 9*b* are summarized in Table 9*c*, having been arranged by age. The number and percentage of children in whom a particular symptom was present for 0, 1, 2, etc., years are stated in Table 10*a*. The number and percentage of children classified in one of the symptom-positive groups for 0, 1, 2, etc., years are shown in Table 10*b*.

The following can be deduced from these tables:

(*a*) The total number of children taking part for five years consisted of 428 of the youngest group (61.1 percent of the initial number) and 389 of the oldest group (55.6 percent). As is

Text-table 2. *Subdivision of D–C-groups*

| Cough | Wheezing | Nasal catarrh | Codes in tables |
|---|---|---|---|
| + | + | + | c+w+n+ |
| + | − | − | c+w−n− |
| + | + | − | c+w+n− |
| + | − | + | c+w−n+ |
| − | + | − | c−w+n− |
| − | − | + | c−w−n+ |
| − | + | + | c−w+n+ |
| − | − | − | c−w−n− |

c(ough) = affirmative answer to questions 1 and/or 2 and/or 3 (1968): questions 1 and/or 2 and/or 3, and/or 4 and/or 5 (1969).
w(heezing) = affirmative answer to question 19 (1968); questions 23 and/or 25 (1969).
n(asal catarrh) = affirmative answer to questions 29 and/or 30 (1968); 34 and/or 35–37, and/or 38, and/or 39–41 (1969).

Text-table 3. *Number and percentage*[a] *of those taking part, 1968–1970*

| | Birth cohort | |
|---|---|---|
| Year | 1960–1961 | 1955–1956 |
| 1968 | 632 (90.2) | 620 (88.5) |
| 1969 | 495 (70.7) | 467 (66.7) |
| 1970 | 466 (66.5) | 439 (62.7) |
| 1971 | 441 (63.0) | 410 (58.5) |
| 1972 | 428 (61.1) | 389 (55.6) |

[a] 700 = 100 %.

apparent from Text-table 3, the largest proportion dropped out after the first survey. There was an equal sex distribution.

(*b*) In the youngest birth cohort, the number of boys included in any of the symptom-positive groups is larger than the number of girls in each year of investigation. The boy-girl ratio in the youngest birth cohort averages 3:2 (Tables 9*a* and 9*b*). In the oldest birth cohort, the number of boys in the symptom-positive groups in 1969, 1971 and 1972 is slightly smaller than is the number of girls, the boy-girl ratio averaging 1:1 in this cohort.

(*c*) *Coughing over prolonged periods* (three or more months a year or three or more consecutive months a year) is most common in six-year-old children (5.6 percent) (Tables 9*a* and 9*c*). In the older age groups, prolonged coughing occurs in only 1–2 percent of the cases, but coughing for three or more months a year is almost twice as common. It should be pointed out that the question asked in 1968 was concerned with prolonged coughing "in the past two years", so that affirmative answers to this question will partly refer to symptoms present at an age of four or five.

(*d*) The prevalence of *coughing for two consecutive months* is higher than is that of coughing for three or more consecutive months but lower than that of coughing for three or more months a year. The prevalence of coughing for one month is approximately twice as high as that of coughing for two months (Tables 9*a* and 9*c*). The number of children coughing for two consecutive months or for one consecutive month shows a marked decrease after the 9th–10th year of life.

(*e*) During the period of life in which the children start smoking (see also p. 26), the prevalence of coughing does not increase.

(*f*) *Dyspnoea.* The symptom "dyspnoea on exertion" shows a marked increase up to roughly 10 percent in the two birth cohorts during 1969 and the following years, whereas the incidence of asthmatic attacks drops to approximately 1 percent or less (Tables 9*a* and 9*c*). This might be partially accounted for by the fact that more effective treatment was instituted as a result of the initial survey, so that genuine attacks of asthma were less common and dyspnoea on exertion became the more outstanding feature. A large proportion of children predisposed to asthma are known to show exercise-induced bronchial obstruction even when the asthma is adequately controlled and attacks no longer occur (20, 24, 30). Unfortunately, this finding could not be verified, as it was not usually possible to obtain a clear picture of the effect of treatment on the course of the symptoms.

(*g*) The prevalence of *rhinitis*, like that of coughing for a short period, decreases after the 9th–10th year of life and occurs then in approximately 6 percent.

(*h*) As is apparent from Table 9*b*, the proportion of children classified into any of the *three symptom-positive groups* varies from approximately 9 to 12 percent in each age group, with exceptions downwards in the 11–12 year range and upwards in the 12–13 year range. These must be assumed to have been due by chance. A striking feature is the fact that no decrease occurs at the age of puberty. The number of children in whom a similar symptom is present in two or more of the five years of investigation is relatively small (Table 10*a*). Among the answers to the questions on cough "three months a year" is most common for

several years, followed by "three consecutive months a year". Coughing for two consecutive months or for one month is only occasionally listed more than once. Among the respiratory symptoms listed in this table, dyspnoea on exertion is most frequently described as having been present for several years.

As was previously apparent from Tables 9*a* and 9*c*, Table 10*a* shows that the prevalence of cough is much lower in the oldest birth cohort than it is in the youngest. This also holds true for attacks of asthma and rhinitis but not for dyspnoea on exertion.

As is shown by Table 10*b*, approximately 2 percent of the children of the two birth cohorts belonged to one of the symptompositive groups for five consecutive years. This was the case with from 2 to 4 percent for four or three years.

*Conclusions*

(1) In most children showing symptoms of prolonged cough, dyspnoea or attacks of asthma, symptom shifts take place over the years. These are not reflected in the transversal prevalence rates.

(2) The symptom-positive groups—the prevalence of which does not vary markedly in the two birth cohorts during the various years of investigation—partly include a varying population. This means that a population of schoolchildren characterized as "positive for CNSRD" in a transversal study may include individuals who will be found to not satisfy the classical criteria of CNSRD when follow-up studies are done in other years.

The reverse also is the case: Section 5.1.2.2. showed that children with recurrent respiratory symptoms are not invariably included in a symptom-positive group in transversal studies when the questionnaire is used in medical history-taking.

In order to gain a better understanding of the significance of these findings, the following relationships were studied:

6.2.1. *The relationship between the frequency of a positive symptom and the previous history of respiratory symptoms*

The findings are shown in Table 11.

All symptoms are characterized by a marked, statistically significant ($P<0.01$ chi-square test) similarity between their appearance in one or several years of investigation and an affirmative answer to questions regarding the previous history. As the number of cases in which a symptom is positive in more than two out of five years is small, it is difficult to decide whether a high incidence of symptoms is more frequently associated with a positive previous history than is a low incidence. This trend is undoubtedly present

The similarity between prolonged cough, dyspnoea on exertion and attacks of asthma on the one hand and periods marked by cough on the other is a very striking feature. This is also the case with previous histories of children with dyspnoea on exertion, attacks of asthma and wheezing and the similarity between histories of attacks of asthma and cough.

*Conclusion.* There is a statistically significant relationship between respiratory symptoms in children at school age and those appearing in previous years.

6.2.2. *The relationship between respiratory symptoms and the pulmonary function parameters one-second forced expiratory volume* ($FEV_{1.0}$) *and the forced expiratory volume expressed as a percentage of the vital capacity* ($FEV_{1.0}\%$). (Tables 12 and 13)

The normal means shown in these tables for the $FEV_{1.0}$, i.e. the $FEV_{1.0}(E)$ were calculated from the findings in the children without recent respiratory symptoms (D − C −, c − w − n −) and with a negative previous history.

The mean $FEV_{1.0}\%$ was 81 ($\pm 10 = 2SE$). The figures listed in Table 13 were achieved by calculation of the mean pulmonary function values for each child from all measurements carried out during the course of the study. (Children in whom less than three measure-

Text-table 4. *Analysis of variance of findings listed in Table 13*

| Cough ≥3 months a year | Cough ≥3 consecutive months a year | Cough 2 consecutive months a year | Cough 1 month a year | Dyspnoea on exertion | Asthmatic attacks | Rhinitis | D+C+ D+C− D−C+ | D−C− and/or n and/or w+ | D−C− c−n−w |
|---|---|---|---|---|---|---|---|---|---|
| $P=0.01$ | $P=0.05$ | $P=0.05$ | $P=0.23$ | $P<0.01$ | $P<0.01$ | $P<0.01$ | $P<0.01$ | $P=0.37$ | $P<0.0$ |

ments were made, were not included in the tables.) The averages were then calculated from the individual averages in each group. Comparison of the children with and without symptoms by age group (Table 12) shows that the mean $FEV_{1.0}$% is usually within one standard error of the normal mean ($\geq 76$ percent) for all symptoms with the exception of asthmatic attacks. Children having asthmatic attacks show a mean $FEV_{1.0}$% within two standard errors of the normal mean up to the fourteenth and fifteenth years of life; however the value decreases with increasing age. The mean $FEV_{1.0}$% is slightly lower in children with symptoms than it is in those without. This is particularly true for asthmatic attacks. Table 13 shows the mean $FEV_{1.0}$% according to the number of years during which a symptom was positive.

In the symptoms prolonged cough (three or more months a year, three or more consecutive months a year, two consecutive months a year), dyspnoea on exertion, attacks of asthma and rhinitis as well as in the symptom-positive combinations, the mean $FEV_{1.0}$ and mean $FEV_{1.0}$% decrease as the number of years in which the symptom or combination of symptoms was present, increase. This trend was verified by an analysis of variance (Text-table 4).

The trend is significant for all symptoms except cough during one consecutive month. The fact that the symptom-negative combination with positive "secondary" symptoms (D–C–, c and/or n and/or w+) does not show variations in pulmonary function indicates that the "secondary" symptoms are indeed of less importance than the major symptoms.

The fact that there is also a significant trend in rhinitis can be understood from Text-table 5, which shows that there is a relationship between the number of years in which rhinitis occurred and that in which other respiratory symptoms were present. This relationship is highly significant for all respiratory symptoms in this table ($P<0.01$; chi-square test).

*Conclusion.* A study of the relationship between various respiratory symptoms and the number of years for which they were present shows that the pulmonary function parameters which were measured decrease with the duration of the symptoms.

This supports the view that these symptoms are relevant as parameters of recurrent or chronic respiratory disorders in children. The effect can be seen already in children who have a major symptom for only one year and it is most marked in children with asthmatic attacks. Prolonged cough, dyspnoea on exertion and the

Text-table 5. *Percentage of children with rhinitis associated with other respiratory symptoms*

| Rhinitis (years) No. of years | Cough ≥3 months a year | | | Cough ≥3 consecutive months a year | | | Dyspnoea on exertion | | | Asthmatic attacks | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | ≥2 | 0 | 1 | ≥2 | 0 | 1 | ≥2 | 0 | 1 | ≥2 |
| 0 | 90.0 | 8.3 | 1.7 | 97.1 | 2.3 | 0.6 | 34.1 | 8.3 | 7.6 | 95.3 | 4.1 | 0.6 |
| 1 | 50.0 | 31.3 | 18.8 | 62.5 | 30.0 | 7.5 | 57.5 | 16.2 | 26.3 | 87.5 | 8.8 | 3.3 |
| ≥2 | 58.2 | 11.4 | 30.4 | 73.4 | 15.2 | 11.4 | 46.8 | 21.5 | 31.6 | 88.6 | 6.3 | 5.1 |

symptom-positive combinations show a similar pattern in this regard. This means that the symptoms referred to must be taken into account in estimating risks, when they have appeared at least once at school age. (See also Section 7.4.)

6.2.3. *The relationship between respiratory symptoms and the histamine threshold*

This is shown in Table 14. Only those children in whom at least three determinations of the histamine threshold were made are included in this table. Each child is arranged in the order of frequency of the various symptoms according to the median value of all histamine thresholds determined in that child.

The question as to whether there is a relationship between the median histamine threshold value and the presence of respiratory symptoms was studied. The relationship between a markedly reduced median value of the histamine threshold (<8 mg/ml) and the presence of symptoms for one or several years is highly significant for each individual symptom and for the symptom-positive combinations ($P < 0.01$, chi-square test). Because of insufficient numbers, this could not be examined for asthmatic attacks.

*Conclusion.* There is a statistically significant relationship between the presence of symptoms and a lowered histamine threshold. This also serves to support the relevance of the symptoms referred to as parameters of chronic or recurrent respiratory disorders in children. The question of whether a histamine threshold showing a permanent decrease has any prognostic significance (see also p. 24) cannot be answered because of the small number of children in whom this was the case. Follow-up studies in a selected population will be better suited for this purpose (26).

## 6.3. COMPARISON OF THE FINDINGS IN HOOGVLIET AND IJSSELMONDE IN RELATION TO AIR POLLUTION

Fig. 6 shows the mean monthly concentrations of sulphur dioxide and smoke in the two districts during the period from 1967 to 1972. As the determinations made in 1968 and the first half of 1969 were unreliable, these are not stated. Beginning in June 1969, air pollution was measured by a semiautomatic apparatus, the so-called merry-go-round. In view of the results of measurements in 1967 and previous years, it was believed that the concentrations of sulphur dioxide and smoke would be much higher in Hoogvliet than in IJsselmonde. However, a chimney which is 213 m high has come into use at the Shell refinery at Hoogvliet in 1969. The differences in air pollution between the two districts turned therefore out to be relatively slight after 1969.

In 1968, there was no appreciable difference in prevalence of symptoms between Hoogvliet and IJsselmonde. Also in the following years, there were no systematic or marked differences between the answers to the questions in the two districts. These answers therefore were not arranged by district in Tables 9–11.

For a summary of the most important literature on the subject of air pollution and respiratory disease, see Appendix IV.

## 6.4. ALLERGY TESTS

The results of the first and second series of skin tests are listed for each birth cohort in Table 15*a*.

The proportion of children of the two birth cohorts in whom the tests were positive showed a two- to threefold increase where house dust, grass pollen and danders were concerned. It comes as no surprise that the proportion of positive tests in the youngest birth cohort in 1973 is of the same order of magnitude as that in the oldest birth cohort in 1968 and 1969. In fifty percent of the children in whom skin tests were positive in both series, the positive test was associated with a lower allergen concentration in the second than it was in the first series. Table 15*b* shows the symptom pattern of the children in whom skin tests were positive in 1973 and that of those in whom all tests were negative.

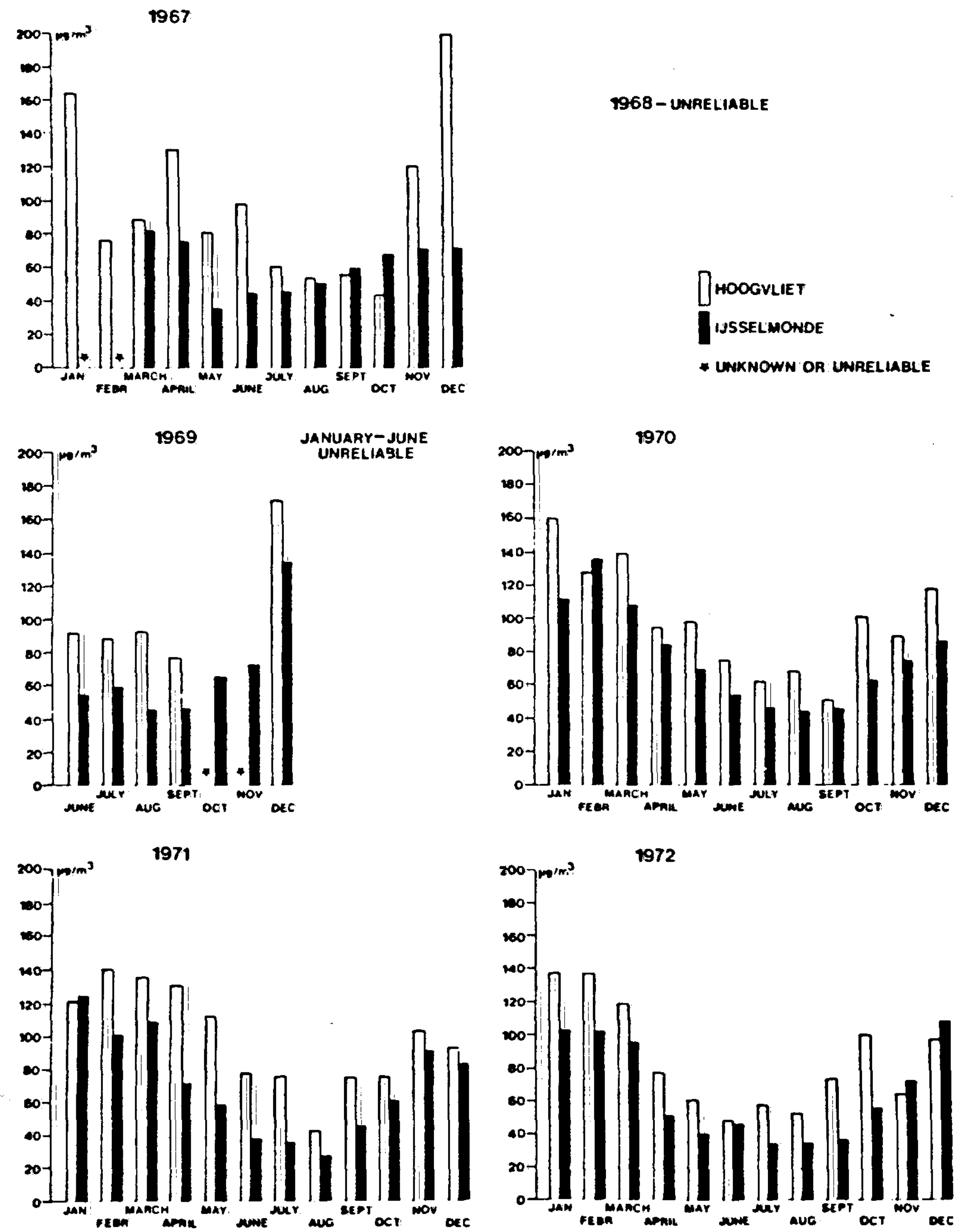


*Fig. 6a.* Mean concentrations of $SO_4$ ($\mu g/m^3$), Hoogvliet and IJsselmonde, 1967–1972.

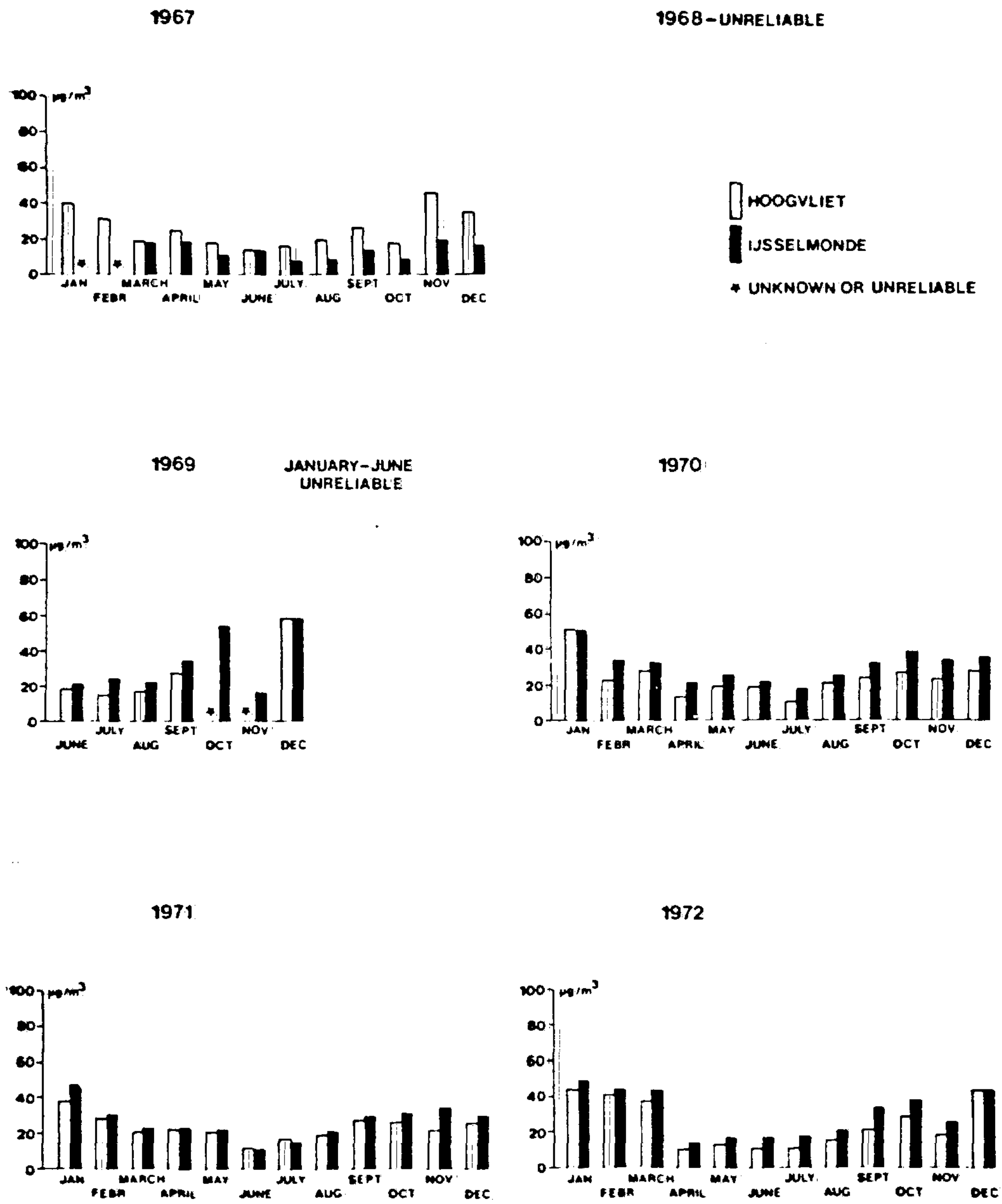


*Fig. 6b.* Mean concentrations of smoke (μm/m³), Hoogvliet and IJsselmonde, 1967–1972.

Text-table 6. *P values of differences in symptom prevalence according to skin tests (chi-square test)*

| Skin test | 1973 | 1968/69 | Cough ≥ 3 months a year | Cough > 3 consec. months a year | Cough 1 and 2 consec. months a year | Dyspnoea on exertion | Rhinitis | D+C+ D+C− D−C+ |
|---|---|---|---|---|---|---|---|---|
| House dust | + <br> − | | n.s. | n.s. | n.s. | $P = 0.02$ | n.s. | $P = 0.04$ |
| | + <br> + | + <br> − | n.s. | n.s. | n.s. | $P = 0.05$ | n.s. | $P = 0.03$ |
| Danders | + <br> − | | $P < 0.01$ | $P = 0.01$ | $P = 0.1$ | $P < 0.01$ | $P < 0.01$ | $P < 0.01$ |
| | + <br> + | + <br> − | $P < 0.01$ | n.s. | n.s. | $P < 0.01$ | $P < 0.01$ | $P < 0.01$ |

The children showing a positive response are arranged according to the allergen used and classified into a "first time negative – second time positive" group and a "twice positive" group.

The chi-square test was used to investigate the significance of differences in symptom-prevalence according to the skintests to house dust and danders[1] (Text-table 6).

Children in whom skin tests to house dust were positive in 1973 showed more often dyspnoea on exertion for one or several years and more often belonged to a symptom-positive group than children in whom skin tests were negative in 1973 ($P < 0.05$). This also was the case with children in whom skin tests to house dust were positive in 1973 and 1968/69 as compared with those in whom skin tests were positive in 1973 but negative in 1968–69 ($P < 0.05$).

Children in whom skin tests to danders were positive in 1973 had all symptoms more frequently than children in whom skin tests were negative in 1973 ($P < 0.01$). But in children with positive skin tests in 1973 and 1968/69 only cough for 3 or more months a year, dyspnoea on exertion and rhinitis were more prevalent than in those with positive tests in 1973 and negative in 1968/69 ($P < 0.01$).

[1] Because of the small number of positives, significance tests have not been done for asthmatic attacks and grass pollen.

*Conclusion.* An obvious relationship exists between the presence of respiratory symptoms and positive skin tests with house dust and danders. This relationship is most marked in the case of danders. This suggests that danders are of greater importance as an allergen than house dust in the population investigated.

A curious finding is the small difference between the proportion of children with positive skin tests to danders who live in households with and without domestic animals (18.0 and 15.6 percent respectively). These latter children obviously have contact with animals so often at school or at their friends' home that they yet become atopic.

### 6.5. RADIOGRAPHY

The number of children with increased line shadows and mottled shadowing is listed in Table 16. The two changes are mainly present in children of the symptom-negative group. Approximately 50 percent of the children with increased line shadows or mottling had a positive previous history.

Other radiological changes were observed in thirteen children. These consisted of:

— marked enlargement of the left hilus in one child. This child had a medical history which was negative for respiratory symptoms and showed a negative tuberculin test
— low diaphragm in four children

— a calcified area in the left upper field in one child
— a broad mediastinal shadow in one child
— an azygos lobe in two children.

### 6.6. RELATIONSHIP BETWEEN SOCIAL AND DEMOGRAPHIC FACTORS AND RESPIRATORY SYMPTOMS

Housing conditions were favourable in the two districts. 54 percent of the children lived in a one-family house. Only 0.4 per cent of the houses were designated as inadequate. The proportion of houses containing one or several damp rooms was 10 percent. 62 percent of the children had their own bedroom, 32 percent shared their bedroom with one child, 6 percent shared it with two or more children. 71 percent of the families kept pets.

There existed no relationship between respiratory symptoms and the occupation of the father, the housing conditions except bedroom shared with two or more, and the presence of pets in the family.

### 6.7. RELATIONSHIP BETWEEN PARENTAL SMOKING AND RESPIRATORY SYMPTOMS IN CHILDREN

Table 17*a* shows the relationship between parental smoking and respiratory symptoms in the children in 1972.

Smoking and nonsmoking parents have about the same proportion of children with respiratory symptoms. The number of cigarettes smoked by the parents has no influence on respiratory symptoms in their children, as is shown in Table 17*b*.

These findings are in accordance with those reported by the majority of other investigators (Appendix V).

### 6.8. RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS IN PARENTS AND CHILDREN

Table 18*a* shows the relationship between respiratory symptoms in parents and children. The more symptoms the parents have, the more of their children belong to one of the symptom-positive groups ($P < 0.01$, chi-square test). Although this is the case in children of smokers and non smokers, it is most obvious in the smokers children, as is apparent from Table 19*b*.

### 6.9. LONGITUDINAL DATA FOR HEIGHT, SKELETAL MATURATION, WEIGHT AND PULMONARY FUNCTION

These will be published separately as soon as the statistical analysis has been completed.

## DISCUSSION OF RESULTS

### 7.1. METHODS

As stated in Section 5.1.2, the answers to the questions posed in the *questionnaire* may be considered as sufficiently reliable for the calculation of prevalence data of respiratory symptoms in schoolchildren. The most common symptom which is the most difficult to evaluate is dyspnoea on exertion. An affirmative answer to the question "Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase" (question 15 (1968), 15 and 18 (1969)) was adopted as a parameter, because question 14 (1968) ("Has your child ever been troubled by shortness of breath when cycling against the wind or on running?") was not considered to be sufficiently specific. The obvious relationship between a previous history of respiratory symptoms and an affirmative answer to this question (Table 11) and the fact that the mean pulmonary function values in children with dyspnoea on exertion were lower than those in children without respiratory symptoms (Tables 12 and 13) sug-



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gests that an affirmative answer should be rated as such. This also holds true for the other major symptoms (cough for three or more consecutive months a year and asthmatic attacks) as well as for the questions cough for three or more months a year, cough for two consecutive months a year and rhinitis. The last three symptoms were included in symptom group D−C− (c+w−n+) to make a differentiation possible between the CNSRD group according to the widely accepted criteria based on studies in adults (36) and symptoms or combinations of symptoms which may be of importance earlier in life. Exercise-induced bronchial obstruction is a common symptom in children (20, 24, 30). Unfortunately, exercise tests using a treadmill or running to determine whether bronchial obstruction particularly occurs in the children with an affirmative answer to the questions on dyspnoea on exertion could not be performed.

Wheezing without prolonged cough, dyspnoea on exertion or asthmatic attacks does not affect pulmonary function. Wheezing has thererefore been classified among the minor symptoms.

Table 13 shows that the $FEV_{1.0}$% was a more sensitive parameter of *pulmonary function* than the $FEV_{1.0}$. This is in accordance with the findings reported by other investigators (22, 46).

In children with symptoms the decrease in pulmonary function was slight and also in those with symptoms for many years, the mean $FEV_{1.0}$% usually was within one standard error of the normal mean in all symptoms with the exception of attacks of asthma. This can be partly due to the fact that—in order to obtain baseline values—measurements were carried out only when respiratory symptoms were not present at the time of investigation and in a season in which few respiratory infections occurred.

Future surveys should include pulmonary function tests revealing changes in the small bronchi, such as determination of the expiratory flow at small lung volumes and the closing volume (8, 16, 35, 40, 41, 55, 56).

Section 5.1.2. shows that *observer's errors* (see also Appendix II) did not affect the answers to the questions to any appreciable extent. The reproducibility of the answers can be considered to be good. The *histamine threshold* is usually regarded as a measure of reactivity of the respiratory tract to nonspecific stimuli (43, 51) and as an endogenous characteristic of chronic nonspecific respiratory disease (52).

However, as de Vries (52) has shown, in adults the histamine threshold is dependent of the initial pulmonary function. As this relationship was rather weak in the children studied, we continued to determine the histamine threshold each year and we have considered it to be an independent characteristic of CNSRD (see also Appendix III).

Surveys for CNSRD showed that a relationship between respiratory symptoms and a lowered histamine threshold ($\leq$ 16 mg/ml) was present in both adults (32) and children (29). The findings in children were verified by the present study.

As stated previously, measurements were carried out only when respiratory symptoms were absent at the time of investigation. This enhances the value of the relationship found to exist between the histamine threshold and a history of respiratory symptoms in regard to the relevance of these symptoms as parameters of chronic or recurrent respiratory disorders.

It is still questionable whether a lowered histamine threshold can be considered as an endogenous characteristic of CNSRD. Only 13 percent of the children in this study showed a diminished median histamine threshold ($\leq$ 16 mg/ml). This is too small a number to answer this question.

The prevalence of a lowered histamine threshold value varied considerably in the various years of investigation (Text-table 7).

This is more in favour of the histamine threshold to be a measure of the reactivity present at the time of investigation than to be an endogenous determined personal characteristic. This is also suggested by the findings in the Dutch alpine clinic for asthmatics in

Text-table 7. *Annual prevalence of histamine threshold*

| Year of investigation | Histamine threshold (mg/ml) | | |
|---|---|---|---|
| | ≤8 % | 16 % | ≥32 % |
| 1968 | 5 | 14 | 81 |
| 1969 | 8 | 16 | 76 |
| 1970 | 1 | 9 | 90 |
| 1971 | 2 | 10 | 88 |
| 1972 | 4 | 7 | 89 |

Davos, where a lowered histamine threshold value is restored to normal levels in some patients, whereas it is not in others during their stay in the high mountains (25, 26).

Patients were examined for the presence of *allergy* by intracutaneous skin tests in which various concentrations of allergen were used as recommended by Voorhorst (50). Some investigators claim that it is preferable to perform skin tests on the back, as the results obtained by this method are believed to be more sensitive and more readily reproducible. This, however, is denied by others (19).

For psychological reasons, the present tests were performed on the volar surface of the right forearm. We used the intracutaneous method since this is more sensitive than the prick test and since the test can be performed with various concentrations of a particular allergen. The fact that reagins to a specific allergen are present in the skin does not imply that bronchial obstruction will occur on inhalation of the allergen (1, 28, 37).

In this survey we found a relationship between the presence of respiratory symptoms and positive skin tests, particularly to danders. This suggests that the increasing practice of keeping domestic animals in families and at schools may result in an increase in respiratory symptoms due to allergy to danders.

During the course of five years, the proportion of children with positive skin tests showed a two- to threefold increase with an increased intensity of the response. This confirms the common finding that antibodies to allergens are to a large extent produced at primary and secondary school age.

*Radiography* was not found to be very useful in differentiating between children with and without respiratory symptoms. This finding is in accordance with that reported by Simon et al. (45). These investigators observed marked radiological changes only in children with severe or moderately severe asthma which continued to cause symptoms.

## 7.2. PREVALENCE

The prevalence rates listed in Tables 8, 9*a*, 9*b*, 9*c*, 10*a* and 10*b* are based on the number of children of population A which took part in the study for a period of five years. The reasons for which children did not take part or no longer participated in the study are stated in section 4.3. These reasons did not include asthma, bronchitis or other respiratory conditions. In Table 20, the prevalence of symptoms in the children of population A in 1968 and 1972 is compared with that of the children who dropped out. The prevalence of symptoms during the last year in which these drop-outs took part in the study was that used in the table. The prevalence rates show only slight differences; the prevalence of symptoms in those who dropped out is slightly lower than it is in those who took part for five years. These may therefore be regarded as a random sample of the children of the two birth cohorts living in Hoogvliet and IJsselmonde on October 1, 1967. The symptom-positive groups include those children who satisfy the criteria of CNSRD applying to adults.

As has been mentioned earlier, the effect of the symptoms cough for three or more months a year and two consecutive months a year on pulmonary function is comparable with that of cough for three or more consecutive months a year. Tables 21 and 22 show the prevalence rates for the children of the symptom-positive groups when the criterion of cough I (C II) is altered from cough for three or more conse-

cutive months a year to cough for three or more months a year and/or two or more consecutive months a year. When these criteria are applied, prevalence increases by 3–4 percent in the two youngest groups and by 1–2 percent in the older groups. The percentage of children included in one of the symptom-positive groups for two or more consecutive years also shows a slight increase. The general prevalence pattern, however, remains almost unchanged. This would not be the case if the symptom "wheezing" were to be added as a criterion for classification within one of the symptom-positive groups. The proportion of children which would then be included in these groups is much higher, as is shown in Table 23. However, as stated on p. 18, "wheezing" may be regarded as a secondary symptom.

Although approximately 50 percent of the children of the oldest birth cohort turned out to be smokers at 14–16 years of age (Table 24), this does not affect the prevalence of symptoms in this cohort.

As stated previously, the increase in the prevalence of the symptom-positive groups, which occurred in the 12th–13th year of life as compared with the previous year, is caused by an increase in the symptom dyspnoea on exertion. This increase is unlikely to have been due to smoking.

The prevalence rates determined in the present study are comparable only in part with those recorded by Knol (29), as this author took the recent and previous histories into account in calculating prevalence. The prevalence rates reported in the present paper were based only on recent histories. Comparison with the prevalence rates reported by others is not possible because of the differences in criteria as has been mentioned in the introduction.

## 7.3. RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND EXOGENOUS FACTORS

### 7.3.1. *Air pollution*

There was no difference between the prevalence of respiratory symptoms in Hoogvliet and that in IJsselmonde. The anticipation, based on the results of measurements carried out in 1967 and previous years, that pollution by sulphur dioxide and smoke during the period of investigation would be much more marked in Hoogvliet than in IJsselmonde was not realized. Therefore, it was not possible to determine whether the prevalence of prolonged cough or dyspnoea increases with the degree of air pollution.

Studies in other areas of the Netherlands (Westland, Zuid-Beveland) have shown that this is actually the case where cough is concerned (6, 27). The problem of short-lived respiratory symptoms resulting from air pollution could not be examined in the present study.

### 7.3.2. *Social and demographic factors*

It has been reported several times in the literature that respiratory symptoms become increasingly common in children as they live in worse social conditions (10, 11, 17).

In order to determine the effect of air pollution under the best possible conditions of life, the study was done in districts marked by an adequate social level. Section 6.6, shows that slight social differences do not affect the prevalence of respiratory symptoms. Providing optimum housing is essential to effective treatment and prevention of chronic or recurrent respiratory symptoms.

### 7.3.3. *Smoking*

Children of the youngest birth cohort may be assumed to be non-smokers. The proportion of children of the oldest birth cohort who stated in an inquiry that they regularly smoked cigarettes was 24 percent in 1970, 51 percent in 1971 and 57 percent in 1972 (Table 24). As these statements were anonymous, the existence of a possible correlation between symptoms and cigarette smoking could not be examined. However, our results showed that the overall-prevalence of respiratory symptoms did not increase at the ages at which regular smoking starts. In accordance with the findings reported by Colley (14, 15) and unlike those reported by a number of other investigators, there was no evidence

that so-called passive smoking due to parental smoking had any appreciable effect on the appearance of respiratory symptoms in school-children. For a review of the literature on smoking and its effects on health in children, the reader is referred to Bewley et al. (4) and to Appendix V.

7.3.4. *Respiratory symptoms in parents*

There is a definite relationship between respiratory symptoms in parents and those in children. This finding is also in accordance with that reported by Colley (14, 15).

Smoking may be taken to cause an increase in respiratory symptoms in the parents and thus indirectly to affect the symptoms in the children. However, repeated studies on the subject as well as a study of the relative contributions of endogenous (genetic) factors (2, 5, 38) and exogenous factors are still required.

## 7.4. LONGITUDINAL TREND

The present study was designed to get an impression of the longitudinal trend of symptoms of CNSRD in each child on the basis of particular features. As was apparent from section 6.2.2, the symptoms will merely cause a slight average decrease in pulmonary function and the mean pulmonary function values usually are within two standard errors of the normal mean values. This means that the pulmonary function parameters adopted ($FEV_{1.0}$, $FEV_{1.0}\%$) are less useful in estimating the trend in each individual than are the symptoms. This also holds true for the histamine threshold, skin allergy and X-rays.

Very few children were found to have shown a particular symptom for more than two years or to have belonged to one of the symptom-positive groups for more than two years. Table 25, however, shows that the respiratory symptoms in a large proportion of these children were less marked in other years. It would therefore appear to be justifiable in principle to regard schoolchildren in whom symptoms of prolonged cough or dyspnoea occur, even if only incidentally, as individuals with "chronic" respiratory disease (which does not imply that this actually is the case with all of these children).

In this context, "chronic" only means that the symptoms recur but does not say anything of the frequency and severity of these symptoms. Although it could be of importance to determine these for reasons of prognosis (42), this cannot be done with the questionnaire used.

In the population studied, therefore, only qualitative measurements of respiratory symptoms were carried out. Only studies in populations followed from childhood up to adult life will be able to show whether any prognostic value can be attached to these measurements. Studies by Colley (12, 13) suggest that this is the case. As the period for which the populations were followed was only five years, it is not possible to form an opinion on this subject as a result of the present study.

On the other hand, efforts were made to gain an impression of the extent to which the previous history is an important factor in the symptom pattern during the period of investigation. For this purpose, the number of times that questions on the previous history were answered in the affirmative or in the negative was studied with regard to the symptoms "cough for three or more months a year", "cough for three or more consecutive months a year", "cough for two consecutive months a year", "cough for one consecutive month a year", "dyspnoea on exertion", "asthmatic attacks" and "rhinitis".

For each of the above symptoms and for eight questions referring to the previous history, the percentage of children answering in the affirmative was divided by that answering in the negative. This quotient represents the relative risk that a symptom which occurred in the previous history will recur in the recent history (7). All of this is included in Table 26 which shows that respiratory symptoms at a young age involve an obvious risk of recurring later in life.

As stated in the introduction, a justifiable opinion on the future course of a "chronic" respiratory condition in the individual child usually cannot be formed. From the point of

view of prevention, it would therefore seem advisable to consider symptoms such as prolonged cough or dyspnoea (regardless of their severity or frequency) in all schoolchildren as potential "risks" of CNSRD in adult life.

This implies that adverse exogenous factors should be avoided wherever possible and that symptoms should be treated by the best possible method. This means in practice:

(1) Prompt treatment of bronchial obstruction and respiratory infections, if necessary daily drug treatment and physical therapy.

(2) Prevention of bronchial obstruction and respiratory infection by avoiding exogenous factors known to be liable to cause symptoms in a particular individual.

(3) Improving housing and adverse social and psychological conditions.

(4) Preventing the children from smoking by personal counseling and health education.

(5) Vocational guidance, counseling on habits of life, etc., if required.

(6) Measles and influenza vaccination.

Controlled screening of children with "chronic" respiratory disease at primary and secondary schools by the school health officer would be advisable. This can be done by using a simple questionnaire. Experience elsewhere (27) showed that a brief questionnaire completed by the parents at home will usually serve the purpose.

Attending physicians (general practitioners as well as specialists) should be more keenly aware of the need for "preventive treatment" than they are today.

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## APPENDIX I. QUESTIONNAIRE

*Text Questionnaire*

[a] Questions concern the past 2 years.
[b] Questions concern the past year.

| | 1968[a] Question number | 1969–1972[b] Question number |
|---|---|---|
| ***I. Cough*** | | |
| Did your child *usually* cough when getting up in the winter? (Usually: that is about 5 days a week.) (Exclude clearing throat or a single cough.) | 1 | 1 |
| Did your child *usually* cough during the day or at night in winter? | 2 | 2 |
| Did your child *usually* cough when getting up in the summer? (Usually: that is about 5 days a week.) (Exclude clearing throat or a single cough.) | — | 3 |
| Did your child *usually* cough during the day or at night in summer? | — | 4 |
| Did your child cough *like this* on most days for as much as three or more month a year? | 3 | 5 |
| Did your child cough *like this* on most days in winter, for as much as three or more consecutive months? | 4 | 6 |
| Did your child cough *like this* on most days in winter, for as much as two consecutive months? | — | 7 |
| Did your child cough *like this* on most days in winter for as much as one consecutive month? | — | 8 |
| Did your child cough *like this* on most days in summer for as muchas three or more consecutive months? | 5 | 9 |
| Did your child cough *like this* on most days in summer for as much as two consecutive months? | — | 10 |
| Did your child cough *like this* on most days in summer for as much as one consecutive month? | — | 11 |
| At what age did your child start coughing? | 6 | — |
| Did your child ever have periods of cough for as much as three consecutive months in the previous years? | — | 12 |
| ***II. Phlegm*** | | |
| Did your child usually bring up phlegm when getting up in winter? | 7 | — |

| | 1968[a] Question number | 1969–1972[b] Question number |
|---|---|---|
| Did your child usually bring up phlegm in winter during the day or at night? | 8 | — |
| Did your child bring up phlegm like this on most days, for as much as three months a year? | 9 | 13 |
| At what age did your child start bringing up phlegm? | 10 | — |
| Did your child in the previous two years have a period of an increase in cough and phlegm lasting for three weeks or more? (Use this formulation for children who usually cough and bring up phlegm.) If "yes" has been answered to this question: | 11 | — |
| Did your child have such a period more than once? | 12 | — |
| ***III. Dyspnoea*** | | |
| Put "1" in square if the child is disabled from walking by any condition other than lung disease. | 13 | 14 |
| Has your child ever been troubled by shortness of breath when cycling against the wind or running? | 14 | — |
| Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase? | 15 | — |
| Has your child regularly been troubled by shortness of breath when playing outdoors or walking up a staircase? | 16 | — |
| Did your child have to stop regularly because of breathlessness and sit down when playing outdoors or walking up a staircase? | 17 | — |
| Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase in winter? | — | 15 |
| Has your child regularly been troubled by shortness of breath when playing outdoors or walking up a staircase in winter? | — | 16 |

*Text Questionnaire* (continued)

| | 1968[a] Question number | 1969–1972[b] Question number |
|---|---|---|
| Did your child have to stop regularly because of breathlessness and sit down when playing outdoors or walking up a staircase in winter? | — | 17 |
| Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase in summer? | — | 18 |
| Has your child regularly been troubled by shortness of breath when playing outdoors or walking up a staircase in summer? | — | 19 |
| Did your child have to stop regularly because of breathlessness and sit down when playing outdoors or walking up a staircase in summer? | — | 20 |
| Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase in the previous years? | — | 21 |
| At what age did you notice for the first time the breathlessness of your child? (Accept "around this age".) | 18 | 22 |
| IV. *Wheezing* | | |
| Did your child ever wheeze in the previous years? | 19 | — |
| Did your child ever wheeze during the past winter? | — | 23 |
| Did your child wheeze most days or nights in winter? | — | 24 |
| Did your child wheeze two times or more? (If "no" proceed to "V *Asthmatic attacks*", if "yes" proceed to the next question.) | 20 | — |
| Does your child wheeze most days or nights? | 21 | — |
| Did your child ever wheeze during the past summer? | — | 25 |
| Did your child wheeze most days or nights in summer? | — | 26 |
| Does your child wheeze all days or nights? | 22 | — |
| At what age did your child start wheezing? | 23 | — |
| V. *Asthmatic attacks* | | |
| When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic attacks)? | 24 | — |

| | 1968[a] Question number | 1969–1972[b] Question number |
|---|---|---|
| When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic attacks) in winter? | — | 27 |
| When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic attacks) in winter in the previous years? | — | 28 |
| When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic attacks) in summer? | — | 29 |
| When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic attacks) in summer in the previous years? (If "no" proceed to "VI *Nasal catarrh*", if "yes" proceed to the next question.) | — | 30 |
| At what age did your child first have these attacks? (Accept "around this age".) | 25 | 31 |
| At what age did your child last have these attacks? (Accept "around this age".) | 26 | 32 |
| Is your child ever short of breath when resting? | 27 | — |
| VI. *Nasal catarrh* | | |
| Did your child ever have a stuffy or a running nose? | — | 33 |
| Has your child usually been troubled by a stuffy nose or nasal catarrh? | 29 | — |
| Have these troubles been present on most days for as much as three or more consecutive months? a. in winter; b. in summer. | 30 | — |
| Has your child usually been troubled by a stuffy nose or nasal catarrh in the past winter? | — | 34 |
| Have these troubles been present on most days for as much as three or more consecutive months in winter? | — | 35 |
| Have these troubles been present on most days for as much as two consecutive months in winter? | — | 36 |
| Have these troubles been present on most days for as much as one month in winter? | — | 37 |

*Text Questionnaire* (continued)

| | 1968[a] Question number | 1969–1972[b] Question number |
|---|---|---|
| Has your child usually been troubled by a stuffy nose or nasal catarrh in the past summer? | — | 38 |
| Have these troubles been present on most days for as much as three or more consecutive months in summer? | — | 39 |
| Have these troubles been present on most days for as much as two consecutive months in summer? | — | 40 |
| Have these troubles been present on most days for as much as one consecutive month in summer? | — | 41 |
| VII. *Previous diseases* | | |
| Did your child ever have: | 36 | 47 |
| Eczema? | 36*a* | 47*a* |
| The tonsils removed? | 36*e* | 47*e* |
| Attacks of bronchitis or asthma? | 36*h* | 47*h* |
| Periods of cough? | 36*i* | 47*i* |
| Pneumonia? | 36*j* | 47*j* |

## APPENDIX II. OBSERVER'S ERRORS

Several investigations have been carried out on the comparability of medical histories taken by various interviewers in an epidemiological study.

*Cochrane and Chapman* (1) differentiate between two potential types of error:

1. Inter-observer's errors: errors appearing as differences between the results obtained by investigators.

2. Intra-observer's errors: errors appearing when the results obtained by a particular interviewer are different when he repeats his study in the same individuals. This is due, among other things, to the fact that one interview may affect the answers given during another interview. Kinsey et al. (4) therefore recommend an interval of at least eight months between two interviews of the same subject.

Cochrane and Chapman (1) had various interviewers question a large number of miners on respiratory and other symptoms. A standardized questionnaire was not used in this case, although efforts were made to standardize the technique of interviewing wherever possible in the survey.

The results obtained by the interviewers showed marked differences as regards the symptoms cough, pain in the chest and dyspepsia. The answers to those questions which had previously been discussed and standardized by the interviewers among themselves (such as the question on exertional dyspnoea) showed less disagreement between the interviewers.

It is concluded by these authors that careful standardization of questions is a condition essential to obtaining comparable results.

Schilling et al. (6) studied medical history-taking and physical examination by two physicians who took turns in examining one half of a group of individuals at a four-month interval. They observed significant differences between the results obtained by the two investigators concerning the results of physical examination and those of history-taking. They believe the differences in the results of history-taking to have been due to the following factors:

1. A difference in the answers given to the same question by the interviewee.

2. The fact that the answer given was influenced by the interviewer.

3. Different interpretations of the same answer by different interviewers. (Standardization of answers does not ensure standardization of interpretation.)

*Fairbairn, Wood and Fletcher* (2) believe that the initial stages of chronic bronchitis can only be recognized by the medical history. If the epidemiology of chronic bronchitis is to be studied, the results of various investigations will have to be comparable. Where medical histories are concerned, comparison will be possible only when a standardized questionnaire is used. The authors carried out a survey in which a standardized questionnaire was employed by six different investigators: three physicians and three health visitors distributed at random over the interviewees. This made it possible to compare the physicians and health visitors as groups and as individual investigators. The interviews were recorded on tapes and played back later. The subjects interviewed were postmen and women sorters in London. They were unselected; their ages ranged from forty to fifty-nine.

Two interviews were conducted at an interval of at least four weeks. Care was taken to prevent the interviewee from being interviewed twice by the same person. In four questions, there were significant differences among the physicians on the one hand and the health visitors on the other.

In thirteen questions, there were significant individual differences among the results. Of these, four were due to differences among the

physicians; the other nine were due to differences among the health visitors.

The differences concern only *affirmative* answers.

Among others, these differences were due to the following causes:

(1) The same interviewees gave different answers to questions put in the same way by the two interviewers.

(2) The health visitors as a group more often rated vague answers as positive than did the physicians as a group.

(3) When a question was answered in the negative, some interviewers asked questions which they should not have asked according to the protocol.

(4) The results suggested that questions which were not put clearly were occasionally answered in the affirmative, even though they had not been properly understood.

(5) The speed with which the interview was conducted influenced the number of affirmative answers, particularly the answers to questions on the previous history of disease.

(6) In a number of cases, the question stipulated was asked in a different (suggestive) manner.

(This mistake was made particularly when the question was formulated in such a way that it was not easy to ask it in a natural manner).

(7) In three per cent of the cases, incorrect recording by the interviewer was the cause of the differences.

*Causes of 149 differences in results in nine questions*

| Cause | Number | Percentage |
|---|---|---|
| Interviewer | 93 | 62 |
| Interviewee | 32 | 21 |
| Question | 24 | 16 |
| | 149 | 100 |

The differences were caused by the interviewers in 62 per cent of the cases; this was mainly due to the fact that they did not stick to the literal wording of the questions. As a result, an unduly large number of affirmative answers was obtained.

The difference between the two most experienced interviewers was as large as that between any other pair of interviewers.

Several investigators (3) (5) (7) are engaged in developing other methods of medical history-taking. The most recent procedure is a questionnaire controlled by a computer.

Questions appear on a screen; the interviewee selects one of four numbered answers: yes, no, I don't know, I don't understand. He presses the corresponding button and, depending on his answer, the computer will either proceed to the following general question or cause a more detailed question on the same subject or some further explanation to appear on the screen. This basic technique is currently being developed to a further extent; among others, by improving understanding and co-operation on the part of the interviewees. In the Mayo Clinic, for instance, the questions are illustrated by drawings. These methods may improve the possibilities of standardization. The answers are immediately ready for processing in the computer. Drawbacks are the considerable expense, the fact that only a limited number of individuals can ben "interviewed" at the same time as well as the fact that errors cannot be traced to their source later on.

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## APPENDIX III. HISTAMINE THRESHOLD AND INITIAL PULMONARY FUNCTION

### INTRODUCTION

Many stimuli having a local action (pharmacological, physical, allergic stimuli) may cause swelling of the mucosa, hypersecretion and contraction of the smooth muscle tissues in the bronchi. The degree of "reactivity" will vary from one individual to another. The histamine threshold or acetylcholine threshold (the lowest concentration of histamine or acetylcholine resulting in a decrease of $\geq 15$ per cent of the vital capacity, or the one-second forced expiratory volume, or other measures of bronchial obstruction) are often adopted as parameters of this reactivity (3).

De Vries (4) pointed out that initial pulmonary function (measured as the one-second forced expiratory volume) and the histamine threshold are not independent of one another. He posed the question whether the histamine threshold may be regarded as a correct parameter of reactivity or whether it merely is an indirect measure of bronchial obstruction. He concluded that, rather than the histamine threshold as such, an index derived from it, the so-called reactivity score might provide a superior parameter of bronchial reactivity.

*Cade and Pain* (1) observed no relationship between the acetylcholine threshold and initial pulmonary function in asthmatic patients free of symptoms. During a symptom-free interval, the acetylcholine threshold was found to be constant over a period of a few weeks.

### METHODS

The relationship between the histamine threshold (3) and the pulmonary function values one-second forced expiratory volume ($FEV_1$), peak expiratory flow (PEF) and vital capacity (VC) was studied in children with chronic nonspecific respiratory disease who attended the outpatient department for respiratory diseases of the Sophia Children's Hospital and in children who took part in the population survey. Follow-up studies were done in these children to determine whether any trend of the histamine threshold values in a particular child is reflected in a similar trend of the pulmonary

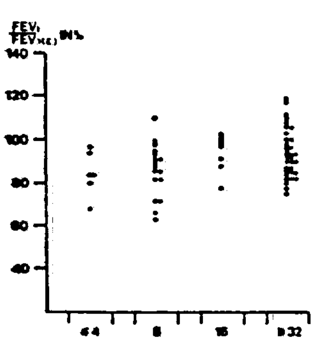


*Fig. 1.* Relationship between $FEV_1/FEV_{1(E)}$ and histamine threshold.

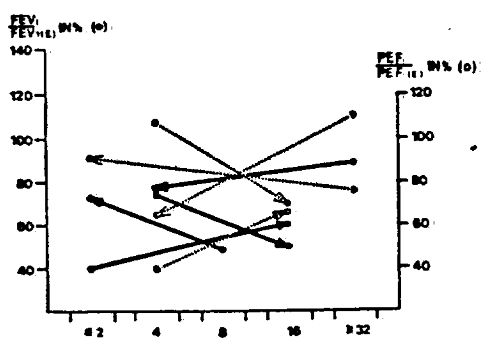


*Fig. 2.* Various relationships between pulmonary function and histamine threshold.

Table 1. *Correlation between histamine threshold and initial pulmonary function in children with chronic nonspecific respiratory disease*

| Histamine threshold (mg/ml) | $FEV_1/FEV_{1(E)}$ [a] | | $VC/VC_{(E)}$ [a] | | $PEF/PEF_{(E)}$ [a] | |
|---|---|---|---|---|---|---|
| | Mean value | Number examined | Mean value | Number examined | Mean value | Number examined |
| ≤ 2 | 0.77 | 12 | 0.97 | 12 | 0.93 | 13 |
| 4 | 0.85 | 18 | 1.03 | 18 | 0.97 | 11 |
| 8 | 0.90 | 7 | 0.99 | 7 | 0.96 | 8 |
| 16 | 1.02 | 2 | 1.12 | 2 | 1.06 | 2 |
| ≥32 | 0.93 | 11 | 0.96 | 11 | 1.18 | 18 |

[a] (E) = height-adjusted mean value according to Polgar (2).

function values during the successive tests performed in that child. This was accomplished as follows. A score also used in Kendall's rank correlation test was calculated for each child per height-adjusted pulmonary function. For the relationship between the histamine threshold and $FEV_1/FEV_{1(E)}$[1], for instance, the following procedure was adopted:

Initially, those children in whom both the histamine threshold and the $FEV_1$ had been determined in more than one study were selected. All tests performed in these children were compared in pairs. When two tests are performed, one paired comparison is possible (1→2, 1→3, 2→3); when four tests are performed, six paired comparisons are possible, etc. A partial score which may assume the values −1, 0 or +1, is added to each paired comparison. This partial score is calculated as follows:

Histamine threshold higher in second test than in first test, $FEV_1/FEV_{1(E)}$ being also higher: +1.

Histamine threshold higher in second test than in first test but $FEV_1/FEV_{1(E)}$ lower:
than in first but $FEV_1/FEV_{1(E)}$ lower: −1.

Histamine threshold lower in second test than in first test but $FEV_1/FEV_{1(E)}$ higher: −1.

Histamine threshold lower in second test than in first test, $FEV_{1.0}/FEV_{1.0}$ exp. also lower: +1.

Histamine threshold and/or $FEV_{1.0}/FEV_{1.0}$ exp. equal in the two tests: 0.

For this purpose, the histamine thresholds were classified into the following groups: ≤4, 8, 16 and ≥32 mg/ml. Two values of $FEV_{1.0}/FEV_{1.0}$ exp. were regarded as being different as soon as they were unequal. Although a difference of two values, ranging from +5 per cent to −5 per cent, does not necessarily mean that there is an actual difference but may be due to variability in the measuring technique, every difference was regarded as an actual difference in calculating the partial score. A longitudinal relationship, if any, will thus be more likely to be detected than it will when values differing from each other by less than 5 per cent are considered to be equal.

The total score of a child for the relationship

[1] $FEV_1/FEV_{1(E)}$ means: one-second forced expiratory volume divided by the height-adjusted mean one-second forced expiratory volume.

$PEF/PEF_{(E)}$ and $VC/VC_{(E)}$ have a similar meaning. The height-adjusted mean values are according to Polgar (2).

Table 2. *Correlation between histamine threshold and initial pulmonary function in a random population of 11-year-old boys and girls*

| Histamine threshold (mg/ml) | $FEV_1/FEV_{1(E)}$ [a] Mean value | $VC/VC_{(E)}$ Mean value | Number examined |
|---|---|---|---|
| ≤ 4 | 0.85 | 0.96 | 6 |
| 8 | 0.86 | 0.90 | 16 |
| 16 | 0.94 | 0.96 | 7 |
| ≥32 | 0.93 | 0.95 | 32 |

[a] See Table 1.

between the histamine threshold and $FEV_1/FEV_{1(E)}$ exp. then will be the sum of the partial scores of all paired comparisons. When two tests have been performed in a child, the total score may therefore assume the values +1, 0 or −1. When three tests have been performed, the total score may assume all the values from −3 up to and including +3, and it may assume all the values from −6 up to and including +6 in the event of four tests.

The same method was used in calculating the total scores of each child for the relationship between the histamine threshold and the $VC/VC_{(E)}$ exp. and, if determined, for the relationship between the histamine threshold and the $PEF/PEF_{(E)}$.

## RESULTS

(1) *Transversal study*

Tables 1 and 2 show the mean initial pulmonary function values for each histamine threshold. There is a linear relationship between the intial value of $FEV_1/FEV_{1(E)}$ or $PEF/PEF_{(E)}$ and the 2 logarithm of the histamine threshold, which is significant at the 5 per cent level test. This means that, starting from the null hypothesis that there is no relationship between the initial pulmonary function value and the histamine threshold, the likelihood that there is a linear trend such as that present in this case or that there is an even more marked linear trend will be smaller than or equal to 5 per cent. Therefore, the null hypothesis at a 5 per cent level has to be rejected. There is no such relationship between the VC and the histamine threshold.

(2) *Longitudinal study*

The total scores per pulmonary function parameter for a number of the children listed in Tables 1 and 2 as well as for a number of other children are shown in Tables 3 and 4. In a large number of cases, this total score is found to be nil. As is shown by Tables 5 and 6, this is usually due to the fact that the value of the histamine threshold is identical in all studies. Therefore, it could not be concluded from these findings that, as a rule, the trend of the histamine thresholds is identical with a similar trend of pulmonary function values during

Table 3. *Scores of histamine thresholds and initial pulmonary functions at repeated examinations, children with CNSRD, number of children*

| | Number of examinations | | |
|---|---|---|---|
| Score | 2 | 3 | 4 |
| $FEV_1/FEV_{1(E)}$* | | | |
| +6 | | | |
| +5 | | | |
| +4 | | | |
| +3 | | 1 | 1 |
| +2 | | 7 | |
| +1 | 4 | 1 | |
| 0 | 13 | 19 | |
| −1 | 9 | | |
| −2 | | 2 | |
| −3 | | | |
| −4 | | | |
| −5 | | | |
| −6 | | | |
| Total number of children | 26 | 30 | 10 |
| $VC/VC_{(E)}$* | | | |
| +6 | | | |
| +5 | | | |
| +4 | | | |
| +3 | | | 2 |
| +2 | | 8 | 1 |
| +1 | 6 | 2 | |
| 0 | 14 | 17 | 7 |
| −1 | 6 | 1 | |
| −2 | | 2 | |
| −3 | | | |
| −4 | | | |
| −5 | | | |
| −6 | | | |
| Total number of children | 26 | 30 | 10 |
| $PEF/PEF_{(E)}$* | | | |
| +6 | | | |
| +5 | | | |
| +4 | | | |
| +3 | | | |
| +2 | | | |
| +1 | 14 | | |
| 0 | 17 | | 1 |
| −1 | 16 | 1 | |
| −2 | | 1 | |
| −3 | | 1 | |
| −4 | | | |
| −5 | | | |
| −6 | | | |
| Total number of children | 47 | 3 | 1 |

* See Table 1.

Table 4. *Scores of histamine thresholds and initial pulmonary functions at repeated examinations in a random population of boys and girls, 11–13 years of age, number of children*

| Score | Number of examinations 2 | 3 | 4 |
|---|---|---|---|
| $FEV_1/FEV_{1(E)}$* | | | |
| +6 | | | |
| +5 | | | |
| +4 | | | 2 |
| +3 | | 1 | 5 |
| +2 | | 2 | |
| +1 | 4 | | 2 |
| 0 | 15 | 6 | 17 |
| −1 | 4 | 1 | |
| −2 | | | |
| −3 | | | 2 |
| −4 | | | |
| −5 | | | |
| −6 | | | |
| Total number of children | 23 | 10 | 28 |
| $VC/VC_{(E)}$* | | | |
| +6 | | | |
| +5 | | | |
| +4 | | | |
| +3 | | 1 | 4 |
| +2 | | 1 | 1 |
| +1 | 5 | | 3 |
| 0 | 15 | 8 | 18 |
| −1 | 3 | | |
| −2 | | | 2 |
| −3 | | | |
| −4 | | | |
| −5 | | | |
| −6 | | | |
| Total number of children | 23 | 10 | 28 |
| $PEF/PEF_{(E)}$* | | | |
| +6 | | | |
| +5 | | | |
| +4 | | | |
| +3 | | 1 | |
| +2 | | 4 | 1 |
| +1 | 5 | 2 | |
| 0 | 22 | 10 | 3 |
| −1 | 5 | | 1 |
| −2 | | 2 | |
| −3 | | | |
| −4 | | | |
| −5 | | | |
| −6 | | | |
| Total number of children | 32 | 19 | 5 |

* See Table 1.

successive studies. This similarity was therefore examined with regard to the VC and $FEV_1$ in twenty and with regard to the PEF in twenty-two children. The results are listed in Table 7. These show that there is usually an adequate relationship between the trend of pulmonary function values and that of the histamine threshold values in the children studied.

## COMMENT AND CONCLUSIONS

Though significant, the relationship between the initial values of the $FEV_1/FEV_{1(E)}$ or PEF/$PEF_{(E)}$ exp. and the initial value of the histamine threshold is rather weak. This is also apparent from Figure 1 in which the initial values of the $FEV_1/FEV_{1(E)}$ of a number of children who took part in the population survey have been plotted against their histamine thresholds. When the histamine threshold of a child is given, the $FEV_1/FEV_{1(E)}$ cannot be even approximately predicted, nor can the histamine threshold of a child be

Table 5. *Number of children examined twice and scoring 0, CNSRD*

| | Histamine threshold | Number |
|---|---|---|
| $FEV_1/FEV_{1(E)}$* | | |
| Higher | Equal | 8 |
| Equal | Higher | |
| Equal | Equal | |
| Equal | Lower | |
| Lower | Equal | 5 |
| Total | | 13 |
| $VC/VC_{(E)}$* | | |
| Higher | Equal | 6 |
| Equal | Higher | |
| Equal | Equal | 1 |
| Equal | Lower | 1 |
| Lower | Equal | 6 |
| Total | | 14 |
| $PEF/PEF_{(E)}$* | | |
| Higher | Equal | 10 |
| Equal | Higher | |
| Equal | Equal | |
| Equal | Lower | |
| Lower | Equal | 7 |
| Total | | 17 |

* See Table 1.

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Table 6. *Number of children examined twice and scoring 0, selected at random*

| | Histamine threshold | Number |
|---|---|---|
| $FEV_1/FEV_{1(E)}$* | | |
| Higher | Equal | 9 |
| Equal | Higher | |
| Equal | Equal | 1 |
| Equal | Lower | |
| Lower | Equal | 5 |
| Total number | | 15 |
| $VC/VC_{(E)}$* | | |
| Higher | Equal | 8 |
| Equal | Higher | |
| Equal | Equal | |
| Equal | Lower | |
| Lower | Equal | 7 |
| Total number | | 15 |
| $PEF/PEF_{(E)}$* | | |
| Higher | Equal | 10 |
| Equal | Higher | |
| Equal | Equal | 1 |
| Equal | Lower | 1 |
| Lower | Equal | 10 |
| Total number | | 22 |

* See Table 1.

predicted when its $FEV_1/FEV_{1(E)}$ is known. The weakness of the relationship between the two quantities is also illustrated in the value for the coefficient of correlation of the $FEV_1/FEV_{1(E)}$ and 2 log of the histamine threshold, viz., 0.32.

As is shown in a number of children in Figure 2, a child showing a histamine threshold which is twice or four times as high in a follow-up study as it was in the initial test may yet show a much lower $FEV_1/FEV_{1(E)}$ or $PEF/PEF_{(E)}$ and vice versa in the second study. Table 7 shows that the trend of the $FEV_1/FEV_{1(E)}$ was the reverse of that of the histamine threshold in eight out of twenty children and that the trend of the PEF/$PEF_{(E)}$ was the reverse of the histamine threshold in six out of twenty-two children. It would therefore appear justifiable to conclude that the histamine threshold value and the pulmonary function values measured in this study were mainly determined by different factors.

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Table 7. *Pulmonary function at first and second histamine threshold, children with CNSRD (number of children)*

| | First histamine threshold compared with second histamine threshold | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | $VC/VC_{(E)}$* | | | $FEV_1/FEV_{1(E)}$* | | | $PF/PF_{(E)}$* | | |
| | Higher | Equal | Lower | Higher | Equal | Lower | Higher | Equal | Lower |
| First histamine threshold at least 2 steps lower than second threshold | 6 | 0 | 3 | 4 | 0 | 5 | 4 | 0 | 8 |
| First histamine threshold at least 2 steps higher than second threshold | 8 | 1 | 2 | 7 | 0 | 4 | 7 | 1 | 2 |

* See Table 1.

## APPENDIX IV. AIR POLLUTION AND RESPIRATORY DISEASE

### 1. INTRODUCTION

There is no consensus regarding the importance of air pollution as a factor in the pathogenesis and course of respiratory disease. A large number of investigators believe, however, that air pollution has an adverse effect.

Pollution of the outdoor air may be caused by:

(1) *Reducing substances.* These mainly consist of sulphur compounds (sulphur dioxide, sulphuric acid and sulphates), smoke and soot. Reducing substances are believed to be the most injurious to health.

(2) *Oxidizing substances.* These mainly consist of hydrocarbons, nitrous oxide and photochemical reaction products (ozone, aldehydes, ketones). Sunlight is required as a catalyst to produce these last-named substances. Oxidizing substances cause irritation of the mucosae of the eyes, nose and throat in susceptible individuals. Although they may induce symptoms in subject with chronic respiratory disease, they apparently affect morbidity and mortality to a lesser extent than do reducing substances.

The air inhaled will be polluted, for instance, by indoor factors under particular conditions of work, when the discharge of products of combustion in houses is inadequate and as a result of smoking. Studies on the effects of short- and long-term exposure to polluted air on the respiratory system is numerous.

The present authors confine themselves to the most important studies on the subject. For a comprehensive review of the literature, readers are referred to the Air Pollution Abstracts (published by the National Air Pollution Control Association) and Environmental Health published by Excerpta Medica.

The following abbreviations have been employed in the present paper:

PEF = peak (expiratory) flow
(F)VC = (forced) vital capacity
$FEV_{1.0}$ = one second forced expiratory volume
$FEV_{0.75}$ = identical with $FEV_{1.0}$ but 0.75 sec instead of one second.

### 2. STUDIES ON THE SHORT-TERM EFFECTS OF AIR POLLUTION

#### 2.1. *In children*

*Anderson and Larsen* (1) studied nonattendance and the incidence of respiratory disease in children in the first form of the primary schools in three localities in British Columbia for a period of six monsths. Two of these localities were adjoining residential areas situated under the smoke of an industry; the third was a non-industrial residential area which was chosen because its climate was comparable with that of the other two. Studies were made to determine whether the incidence of respiratory disease was higher in the two first-named areas. There was no significant difference in school absences among the three residential areas but respiratory infections and other forms of disease were more common and more prolonged in the children living in the polluted areas than they were in those living in the nonpolluted area; peak flow values were also significantly lower in the children living in the polluted areas.

*Lunn et al.* (20) studied 819 Sheffield infant school children living in districts in which the degree of air pollution (sulphur dioxide and smoke) differed widely. Infections of the upper as well as those of the lower respiratory tract were found to be more common in the more polluted districts. Socioeconomic factors such as social class, size of the family and housing were of minor importance. Pulmonary function parameters ($FEV_{0.75}$ and FVC) were not

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affected by socioeconomic factors or air pollution, except in the most severely polluted area, where these pulmonary function values showed a significant decrease. Four years later, follow-up studies were done in 558 of these children at the age of 9 (21). Respiratory symptoms were less common than they had been four years previously and there were no longer any differences among the various residential districts. These improvements were accompanied by a decrease in the overall air pollution level in Sheffield and a reduction in the differences in air pollution among the districts themselves.

*Girsh* et al. (11) studied the relationship between weather conditions and air pollution on the one hand and peaks in the incidence of attacks of asthma on the other by recording the number of patients with attacks of asthma attending the out-patient department of a Philadelphia children's hospital daily for two years. This number was three times as high on days marked by a measurable increase in air pollution (sulphur dioxide, nitrous oxide, carbon monoxide and soot). Attacks of asthma were four times as common on days marked by a high atmospheric pressure as they were on days marked by a low atmospheric pressure. During the period of investigation, high atmospheric pressure accompanied by increased air pollution was present on 117 days. The incidence of attacks of asthma on these days showed a ninefold increase compared with that on days on which the air was cleaner and less stagnant.

*Ferris* (9) studied school absences in approximately 700 first and second graders of seven primary schools in Berlin (New Hampshire) over a period of eighteen months. The schools were situated in areas in which air pollution (sulphur dioxide and smoke) differed markedly. Differences in school absence were not observed. However, the PEF, FVC and $FEV_{1.0}$ values measured during the second period of investigation were significantly higher than were those in children of schools in the nonpolluted districts. This was not adequately accounted for by differences in social class. The author believes that the differences in pulmonary function values may have been due to differences in air pollution (see also 24).

*Chiaramonte* et al. (5) studied 429 children attending the emergency room in the children's ward of Long Island College Hospital, New York for three weeks, which included a few days with a marked increase in air pollution (sulphur dioxide). Eighty-three of these children showed respiratory conditions; the majority were hospitalized during or just after the period of air pollution. The number of children admitted for obstructive respiratory disease was larger during or just after the air pollution peak than it was during the other periods. The differences were statistically significant.

*McMillan* et al. (22) studied pulmonary function in third graders of two primary schools in two towns marked by different degrees of air pollution (sulphur dioxide, nitrous oxide, soot). Pulmonary function values (PEF) were measured by a peak-flow meter twice monthly for eleven months, invariably at 1 p.m., the time at which the concentration of oxidant air pollution was believed to be highest. The studies were done to examine whether:

(1) Sudden changes in oxidant air pollution are associated with changes in PEF. There was no evidence to suggest that this was so. There was a constant difference between the mean PEF in the children of the two schools but a decrease in mean PEF was not associated with an increase in air pollution in either of the two groups.

(2) Prolonged exposure to air pollution is associated with a permanent decrease in PEF. The mean PEF in the children attending the school in the most severely polluted area was found to be constantly higher than it was in those attending the school in the less severely polluted area.

(3) Symptoms of infection of the upper respiratory tract are associated with prolonged exposure to air pollution. The incidence of infection of the upper respiratory tract was almost three times as high in children attending the school in the less severely polluted area.

### 2.2. *In adults*

*Lawther* et al. (17) studied the relationship between respiratory symptoms and air pollution in cases of chronic bronchitis in London by having the patients record their symptoms every day. The sulphur dioxide and smoke concentrations were measured at seven points in Inner London; the patients all lived or worked in Greater London. In 1959–1960, a positive relationship between air pollution and an increase in symptoms during the early part of the winter was found (November). This relationship was no longer present at the end of the winter (February). This survey, which was carried out for the first time during the winter of 1954 to 1955, is now being repeated in London every five years.

For a period of six months, *Shy* et al. (24) studied the incidence of acute respiratory disease in families having a child attending an elementary school as a second grader. The studies were done in four districts of Greater Chattanooga: one in which air pollution by nitrous oxide was very severe, another which was polluted by particles floating high in the air and two "clean" areas. More cases of respiratory disease were constantly observed in the two first-named areas, particularly during the outbreak of influenza A2. This difference in the incidence of acute respiratory disease in the various areas could not be accounted for by the family constellation or social class.

As part of a triennial follow-up study of the populations of Vlagtwedde and Vlaardingen, *Van der Lende* et al. (18) studied the VC and $FEV_{1.0}$ in Vlaardingen during a short period of increased air pollution in October 1969 and compared the findings with those during a period of low air pollution. They observed a transient decrease in VC and $FEV_{1.0}$ during this period. These authors conclude that spirometry probably is a more sensitive method than medical history-taking in measuring the effects of air pollution peaks.

## 3. STUDIES ON THE LONG-TERM EFFECTS OF AIR POLLUTION

### 3.1. *In children*

*Douglas* and *Waller* (8) studied 3 866 children from birth in 1946 up to the age of 15 (1961). These children had been living in 2 689 different residential areas since their birth. Each of these residential areas was classified into one of four categories according to the degree of air pollution (sulphur dioxide and smoke). The results were simple and constant in character: conditions of the upper respiratory tract were not affected by the degree of air pollution but the incidence and severity of diseases of the lower respiratory tract were greater in those areas in which air pollution was more severe. This correlation was present at every age. There was no difference between the sexes or between different social classes.

*Biersteker* (3) observed no difference between the height-adjusted mean peak flow rate in 500 Rotterdam school children living in a central district in which air pollution (sulphur dioxide and smoke) was relatively severe and that in 500 school children living in a nonpolluted suburban district.

*Holland* et al. (13) studied 10 971 children in four Kent districts showing various degrees of air pollution (sulphur dioxide and smoke). The mean PEF in children living in the most severely polluted area was lower than that in children living in the less severely polluted areas. This was independent of social class, size of the family and previous respiratory disease (which also was a factor in itself). It is concluded from these findings that air pollution probably results in changes in the respiratory tract during childhood. These changes possibly continue to be present throughout life and may contribute to the subsequent development in chronic respiratory disease.

*Shy* et al. (24), who studied second graders in four districts of Greater Chattanooga marked by different degrees of air pollution (nitrous oxide), found the $FEV_{0.75}$ to be lower in children in the district showing the highest degree of

pollution than it was in children living in the "clean" control areas.

*Colley* and *Reid* (7) studied over 10 000 6–10-year-old children in various districts of England and Wales which showed different degrees of air pollution (sulphur dioxide and smoke). Previous histories of chronic cough, disease of the upper respiratory tract and "bronchitis" were more common in the lower than they were in the higher social classes. The prevalence of chronic cough and disease of the upper respiratory tract increased with the local degree of air pollution only in the children of social classes IV and V (unskilled and semi-skilled workers).

*Sultz* et al. (26) studied 617 children hospitalized for asthma over a period of five years and found air pollution to increase the incidence and severity of attacks of asthma.

*Zapletal* et al. (27) studied the effect of air pollution (sulphur dioxide) on various parameters of pulmonary function in 111 children showing no respiratory symptoms and who had been living in a highly polluted area for at least five years. The FVC, $FEV_{0.75}$ and $FEV_{1.0}$ were within normal limits in all children. Six children with a low normal FEV showed a reduced expiratory flow when the vital capacity was low. This is indicative of obstruction of the respiratory tract. As these children had had no recent or previous respiratory disease in so far as this could be verified, the authors believe that the obstruction of the bronchi may have been due to air pollution.

*Shy* et al. (25) studied pulmonary function ($FEV_{0.75}$) in children attending primary schools in areas marked by high and low degrees of air pollution in Cincinatti, Chattanooga and New York (suspended particles, sulphur dioxide and nitrous oxide). There was a constant relationship between diminished pulmonary function in 5–13-year-old children and exposure to air pollution. In Cincinnatti, pulmonary function improved during periods of slight air pollution but failed to increase to the level of those living in areas constantly marked by only a small degree of pollution. The findings in 9–13-year-old children in New York showed that exposure to high degrees of air pollution in early childhood for periods ranging from five to ten years may result in a prolonged decrease in $FEV_{0.75}$.

In Chattanooga, the effect of exposure to an increased concentration of nitrous oxide for a period varying from two to three years was not measurable to any appreciable extent.

*Grosse* et al. (12) studied the relationship between air pollution and pulmonary function in 1 930 school children in two towns in the German Democratic Republic showing different degrees of air pollution (sulphur dioxide and smoke) in 1970. Children living in the most highly polluted area usually showed a decrease in VC and FEV values.

As part of the Euro 3114 project of the WHO in Copenhagen, *Kerrebijn* and *Biersteker* (15) did a study on children in the Westland area of the Netherlands. Here, there is a high degree of exposure to sulphur dioxide as a result of the fact that a large number of hothouses are heated with sulphurous oil. The results were compared with those obtained in children living in an area in which exposure to sulphur dioxide is low. About 2 400 children of the fourth and fifth forms of the primary school in the two areas, participated in the study which took place in the spring and early summer of 1973. The findings showed that the symptoms wheezing and rhinnorrhoea and the appearance of bronchitis or pneumonia were commoner in the polluted areas. The mean $FEV_{0.75}$ and FVC were also found to be lower in the polluted districts.

### 3.2. *In adults*

*Oshima* et al. (23) studied the effect of air pollution (sulphur dioxide) on the respiratory tracts of Japanese subjects in an area marked by a relatively low degree of pollution (Niigata) and compared this effect with that in a similar population group in an area showing a high degree of pollution (Tokyo, Yokohama). Pulmonary function tests were performed (FVC and $FEV_{1.0}$); 2 765 subjects took part in this study. The inhabitants of Tokyo and Yoko-

hama produced larger quantities of sputum and more frequently showed chronic cough and irritation of the throat. Of these, cigarette smokers and subjects having previous histories of allergy showed the largest number of symptoms. The mean FVC was lower in the inhabitants of this area than it was in the inhabitants of Niigata, and this was particularly so in those who had been living in Tokyo and Yokohama for a considerable period.

*Holland* and *Reid* (14) studied the incidence of respiratory symptoms, sputum production and pulmonary function ($FEV_{1.0}$ and PEF) in the drivers of mail and delivery vans in the city of London and the towns of Gloucester, Peterborough and Norwich. Particularly from the age of fifty, symptoms were more common and more severe in the Londoners; they produced larger average quantities of sputum and showed lower mean pulmonary function values. There was a definite relationship between personal smoking habits and the incidence and severity of the symptoms in each population studied. However, the difference between urban and rural smoking habits failed to account for the higher incidence of respiratory symptoms in London. It is concluded by the authors that this higher incidence of symptoms was due mainly to the difference in air pollution (sulphur dioxide) between central London and the three country towns.

*Biersteker* (2) examined 1 000 Rotterdam municipal officers for symptoms of bronchitis. He observed a number of subjects showing bronchitis; the number increased with age. Those affected with bronchitis smoked a significantly larger number of cigarettes than did those free of bronchitis. The average period for which they had been living in Rotterdam (adopted as a measure of exposure to air pollution) did not differ in those with and those without symptoms.

*Lambert* and *Reid* (16) studied the incidence of respiratory disease in 9 975 men and women in the 35–69 year range using a postal questionnaire. Chronic respiratory symptoms were found to be more common in smokers and to increase with age. Men showed symptoms more frequently than women (both smokers and nonsmokers). The differences between urban and rural areas were not solely accounted for by differences in smoking habits. Air pollution (sulphur dioxide and smoke), however, apparently did not affect nonsmokers to an appreciable extent. There seems to be an interaction between smoking and air pollution, resulting in an increased prevalence of respiratory disease in smokers living in highly polluted areas. This becomes particularly apparent with increasing age.

*Cohen* et al. (6) studied the incidence of cough, sputum production and a number of pulmonary function parameters in two comparable groups of nonsmoking adults permanently exposed to identical mean but different peak degrees of air pollution (sulphur dioxide, nitrates, sulphates). There were no significant differences between the two groups.

*Ferris* et al. (10) reported the results of a follow-up study of adults in Berlin, New Hampshire, in 1961 and 1967. Even when the effects of ageing and changes in smoking habits were taken into account, cases of respiratory disease were found to be less common in 1967. The fact that the average results of pulmonary function studies (FVC and $FEV_{1.0}$) in 1967 were superior to those obtained in 1961 was in accordance with this finding. Air pollution (sulphur dioxide and soot) was less marked in 1967 than it was in 1961. The authors believe that this accounts for the decrease in the incidence of respiratory disease and the improvement in pulmonary function values.

Since 1965, *Van der Lende* et al. (19) have been doing comparative follow-up studies on the incidence of chronic nonspecific respiratory disease among the inhabitants of a rural area (Vlagtwedde) and those of an air-polluted area (Vlaardingen). The pollutants are sulphur dioxide, soot, nitrous oxide and hydrocarbons. The studies also include "micropollution" in the two environments (smoking habits, occupational activities, type of heating, etc.). The prevalence of chronic cough and expectoration